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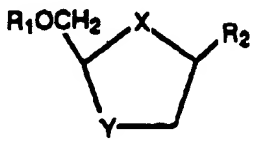
(54) Title: SUBSTITUTED 1,3-OXATHIOLANES AND SUBSTITUTED 1,3-DITHIOLANES WITH ANTIVIRAL PROPERTIES



(1)

(57) Abstract

This invention relates to novel substituted 1,3-oxathiolanes and substituted 1,3-dithiolanes of formula (I) wherein X is S, S=O, or SO_2; Y is O, S, S=O, or SO_2; R_1 is hydrogen, trisubstituted silyl, substituted r unsubstituted C_{1-6} alkyl, substituted r unsubstituted aralkyl, or substituted or unsubstituted C_{1-16} acyl; and R_2 is a purine or pyrimidine base or an analogue or derivative thereof; and pharmaceutically acceptable derivatives thereof. This invention also relates to processes for preparing these compounds, intermediates useful in their preparation, to pharmaceutical compositions containing them and to the use of these compounds as antiviral agents.

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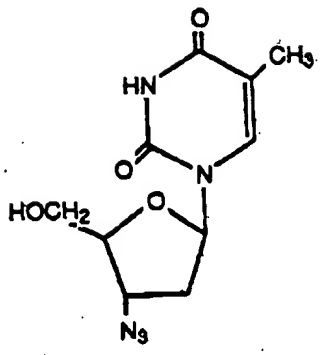
SUBSTITUTED 1,3-OXATHIOLANES AND SUBSTITUTED 1,3-DITHIOLANES WITH ANTIVIRAL PROPERTIES

The present invention relates to novel substituted 1,3-oxathiolane and substituted 1,3-dithiolane compounds having pharmacological activity, to intermediates useful in their preparation, to pharmaceutical compositions containing them, and to the use of these compounds in the antiviral treatment of mammals.

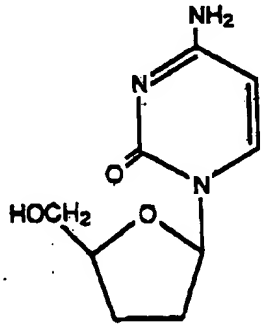
Retroviral infections are a serious cause of disease, most notably, the acquired immunodeficiency syndrome (AIDS). The human immunodeficiency virus (HIV) has been recognized as the etiologic agent of AIDS. Compounds having an inhibitory effect on HIV multiplication or otherwise effective in the therapy of retroviral infections are being actively sought.

H. Mitsuya et al., "3'-Azido-3'-deoxythymidine (BW A509U): An antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus in vitro", Proc. Natl. Acad. Sci. U.S.A., 82, pp. 7096-7100 (1985), refers to 3'-azido-2',3'-dideoxythymidine of formula (A), commonly referred to as AZT. This compound is said to be useful in providing some protection for AIDS carriers against the cytopathogenic effect of immunodeficiency virus (HIV).



(A)

H. Mitsuya and S. Broder, "Inhibition of the in vitro infectivity and cytopathic effect of human T-lymphotrophic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) by 2',3'-dideoxynucleosides", Proc. Natl. Acad. Sci. U.S.A., 83, pp. 1911-15 (1986), have also referred to a group of 2',3'-dideoxynucleosides shown in formula (B) which are said to possess protective activity against HIV-induced cytopathogenicity.

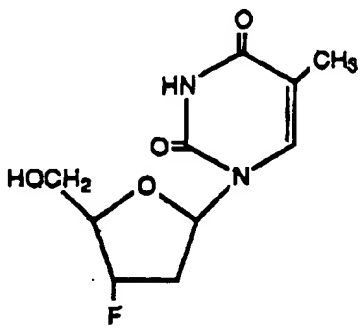


(B)

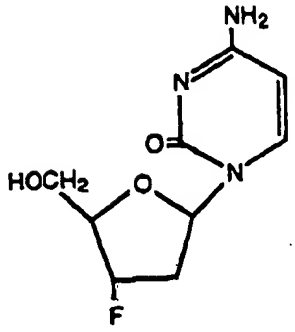
P. Herdewijn et al., "3'-Substituted 2',3'-dideoxynucleoside analogues as potential anti-HIV(HTLV-III/LAV) agents", J. Med. Chem., 30, pp. 1270-1278 (1987), describe the anti-HIV activity of a series of 3'-substituted nucleoside analogues. While 3'-fluoro analogues of 2',3'-dideoxythymidine and 2',3'-dideoxycytidine shown in formulas (C) and (D) are found to possess potent antiretroviral activity, substituents

linked to the 3'-carbon via a thio or oxygen bridge did not yield active products.

(C)

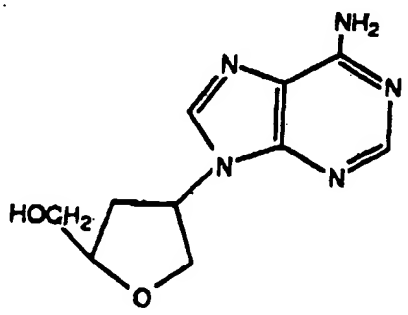


(D)



Analysis of molecular conformation studies in P. Van Roey et al., "Correlation between preferred sugar ring conformation and activity of nucleoside analogues against human immunodeficiency virus", Proc. Natl. Acad. Sci. U.S.A., 86(10), pp. 3929-3933 (1989), indicate that active anti-HIV nucleoside analogues have 3' carbon conformations on the side opposite to the base.

D. Huryn et al., "Synthesis of iso-ddA, member of a novel class of anti-HIV agents", Tetrahedron Lett., 30(46), pp. 6259-6262 (1989), refer to the iso-nucleoside analogue of formula (E) as a stable inhibitor of HIV replication.

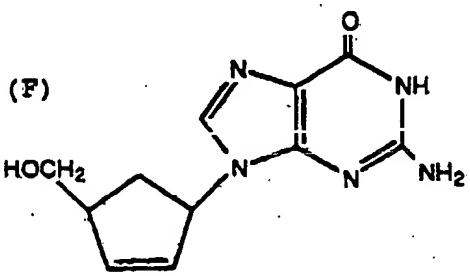


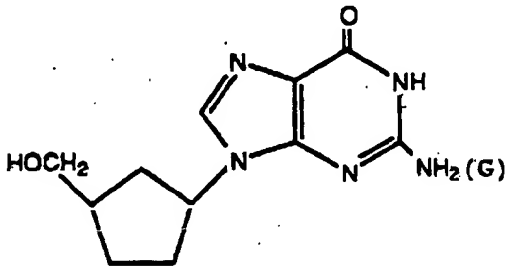
(E)

R. Vince and M. Hua, "Synthesis and anti-HIV activity f carbocyclic 2',3'-didehydro-2',3'-dideoxy

2,6-disubstituted purin nucleosides", J. Med. Chem., 33(1), pp. 17-21 (1990), describe the analogues shown in formulas (F) and (G) as having anti-HIV activity. The unsaturated analogue (F) shows greater selectivity and potency as an inhibitor of HIV replication than the saturated analog (G).

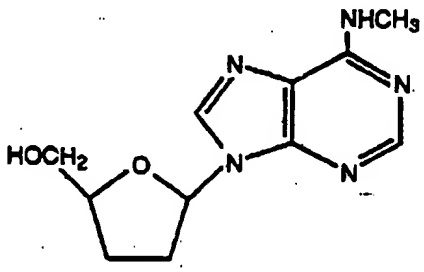
(F)





(G)

C. Chu et al., "Synthesis and structure-activity relationships of 6-substituted 2',3'-dideoxypurine nucleosides as potential anti-human immunodeficiency virus agents", J. Med. Chem., 33(6), pp. 1553-1561 (1990), describe the N_6-methyl derivative shown in formula (H) as having greater potency against HIV than unmethylated 2',3'-dideoxyadenosine.



(H)

Finally, B. Belleau et al., "Design and activity of a novel class of nucleoside analogues effective against HIV-1", Abstracts of papers, Fifth International Conference on AIDS, Montreal, T.C.O. 1,

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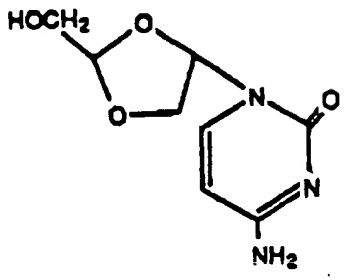
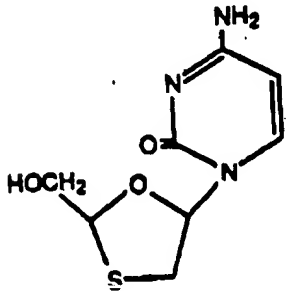
p. 515 (1989), r fer to dioxolanes and oxathi lanes of formulas (J) and (K) as having potent anti-HIV activity.

(J)



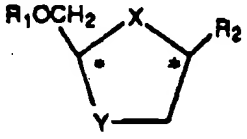


(K)

Despite these developments to date, and in view of the increasing incidence and life threatening characteristics of AIDS, there is a great need for the discovery and development of new potent and non-toxic inhibitors of HIV.

Two structurally distinct classes of compounds known as 2-substituted 4-substituted 1,3-oxathiolanes and 2-substituted 4-substituted 1,3-dithiolanes have been found to have potent antiretroviral activity. In particular, these compounds have been found to act as potent inhibitors of HIV-1 replication in T-lymphocytes over a prolonged period of time with less cytotoxic side effects than compounds known in the art. These compounds are also useful in prophylaxis and treatment of hepatitis B virus infections.

There are accordingly provided in a first aspect of this invention compounds of formula (I)



(I)

wherein X is S, S=O, or SO_2;

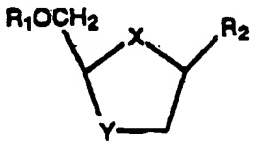
Y is O, S, S=O, or SO_2;

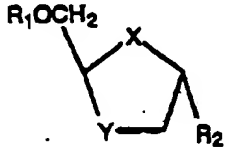
R_1 is hydrogen; and

R_2 is a purine or pyrimidin base or an analogue or derivative there f; and
pharmaceutically acceptable derivatives thereof.

It will be appreciated by those skilled in the art that the compounds of formula (I) contain at least two chiral centers (shown as * in formula (I)) and thus exist in the form of two pairs of optical isomers (i.e., enantiomers) and mixtures thereof including racemic mixtures. Thus the compounds of formula (I) may be either cis isomers, as represented by formula (II), or trans isomers, as represented by formula (III), or mixtures thereof. Each of the cis and trans isomers can exist as one of two enantiomers or as mixtures thereof including racemic mixtures. All such isomers and mixtures thereof including racemic mixtures are included within the scope of the invention.

(II)



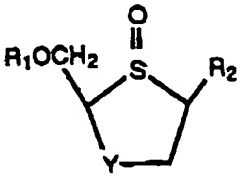


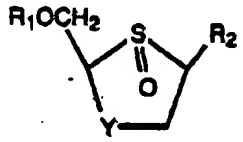
(III)

The compounds of formula (I) are preferably in the form of their cis isomers.

It will also be appreciated that when X is S=O and Y is O, S, or SO_2, the compounds exist in two additional isomeric forms as shown in formulas (IIa) and (IIb). These isomers differ in the configuration of the oxide oxygen atom relative to the 2,4-substituent.

(IIa)





(IIb)

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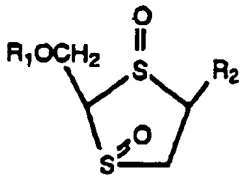
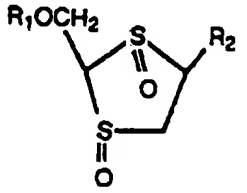
It will be further appreciated that when X is S=O and Y is S=O the compounds exist in four additional isomeric forms as shown in formulas (IIc)-(IIf). These isomers differ in the configuration of the oxide oxygen atom relative to the 2,4-substituent. Similar isomeric forms exist for the trans compounds of formula (III).

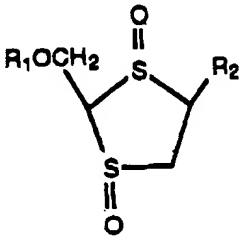
(IIc)

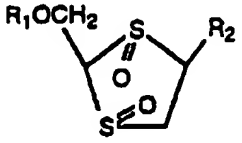




(IId)

(IIe)





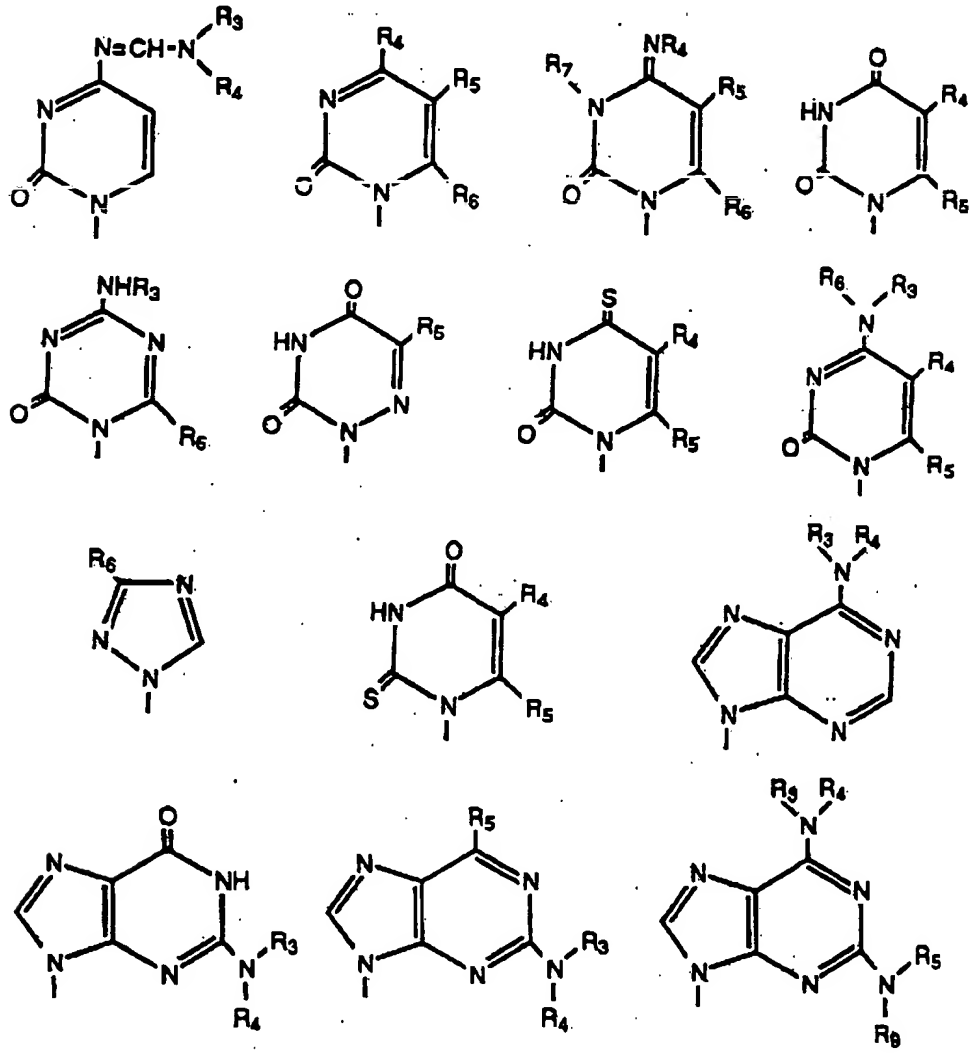
(IIf)

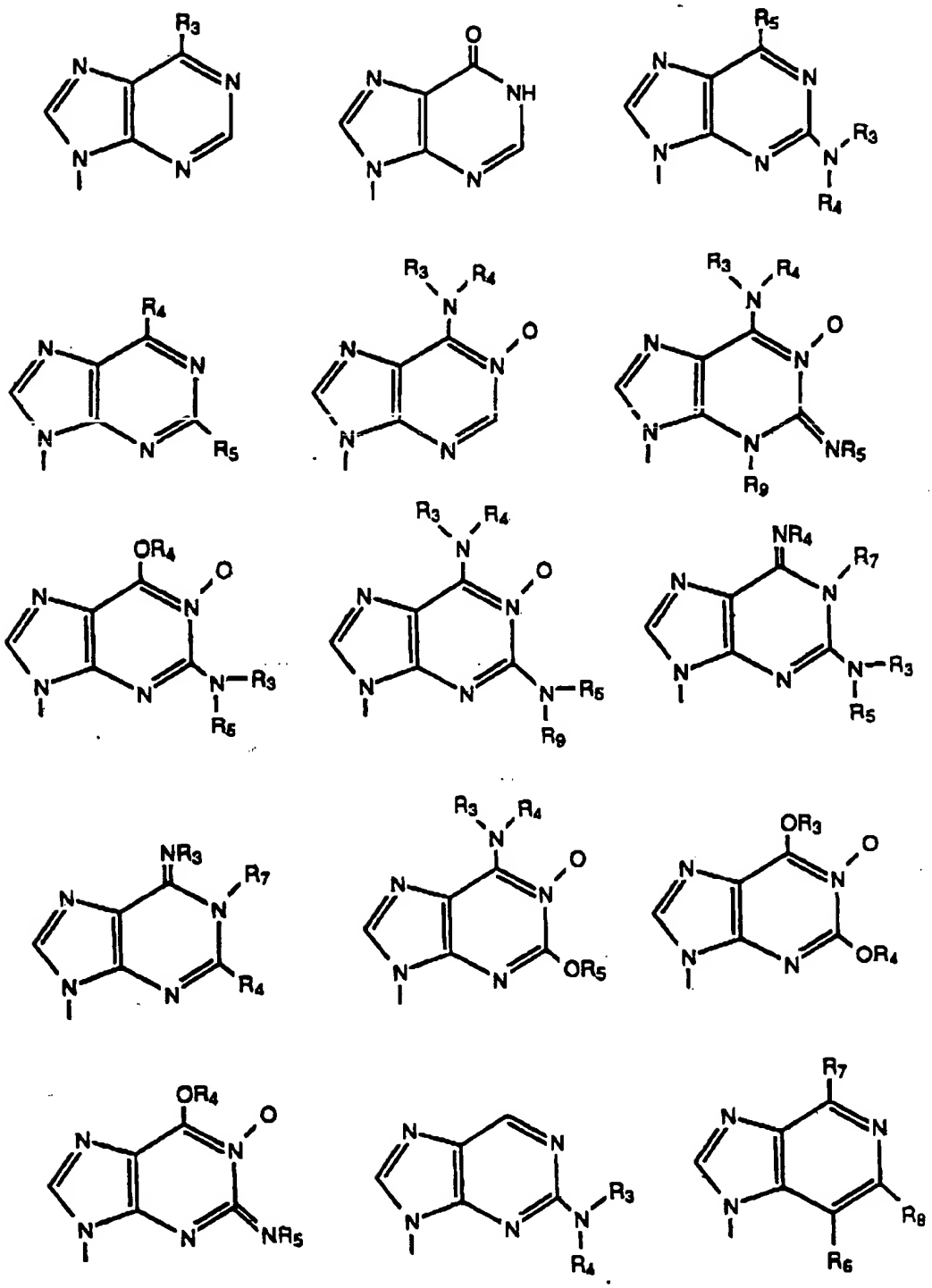
The compounds of the invention additionally embrace such isomers and mixtures thereof.

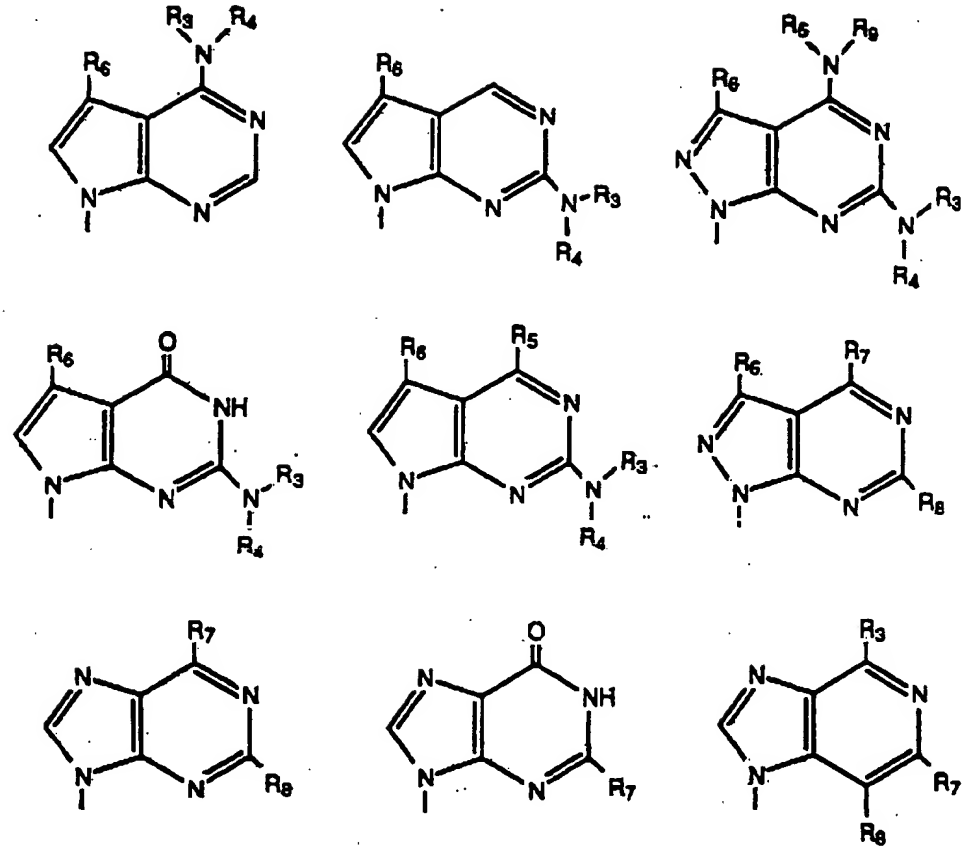
The R_2 purine or pyrimidine base or analogue or derivative thereof, depicted in formula (I), will be linked at the 9- or 1- position respectively. By purine or pyrimidine base or analogue or derivative thereof is meant a purine or pyrimidine base found in native nucleosides or an analogue thereof which mimics such bases in that their structures (the kinds of atoms and their arrangement) are similar to the native bases but may either possess additional or lack certain of the functional properties of the native bases. Such analogues include those derived by replacement of a CH moiety by a nitrogen atom (for example, 5-azapyrimidines such as 5-azacytosine) or vice verse (for example, 7-deazapurines, such as 7-deazadenine or 7 deazaguanine) or both (e.g., 7-deaza, 8-azapurines). By derivatives of

such bases or analogues ar meant those compounds wherein ring substituents are either incorporated, removed, or modified by conventional substituents known in the art, e.g., halogen, hydroxyl, amino, C_{1-6} alkyl. Such purine or pyrimidine bases, analogues and derivatives will be well known to those skilled in the art.

Conveniently the group R_2 is selected from:







wherein R_3 is selected from the group of hydrogen, C_{1-10} acyl (e.g., acetyl), hydroxyl, substituted or unsubstituted C_{1-6} alkyl, and substituted or unsubstituted C_{1-6} alkenyl or alkynyl (e.g. propynyl);

R_4 and R_5 are independently selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkenyl or alkynyl, bromine, chlorine, fluorine, iodine, and thioaryl;

R_6 is selected from the group of hydrogen, bromine, chlorine, fluorine, iodine, cyano, carboxy, carboxamide, ethoxycarbonyl, carbamoyl, and thiocarbamoyl;

R_7 and R_8 are independently selected from the group of hydrogen, bromine, chlorine, fluorine, iodine, substituted or unsubstituted amino, and hydroxy; and

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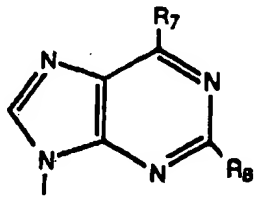
R_9 is selected fr m the group of hydrog n, C_{1-10} acyl, hydroxyl, substituted or unsubstituted C_{1-6} alkyl, and substituted or unsubstituted C_{1-6} alkenyl or alkynyl; and pharmaceutically acceptable derivatives.

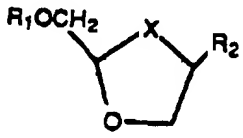
Preferably R_2 is



wherein R_7 and R_8 are as defined above.

Y is preferably -O-.

The preferred 2-substituted 4-substituted 1,3-oxathiolane of this invention is a compound of formula (Ia):

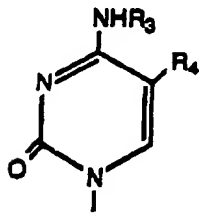


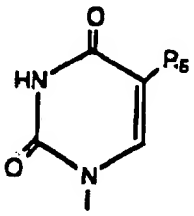
(Ia)

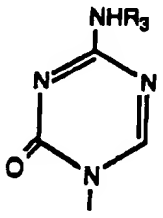
wherein X is S, S=O, or SO_2;

R_1 is hydrogen,; and

preferably, R_2 is a heterocyclic radical selected from the group consisting of:







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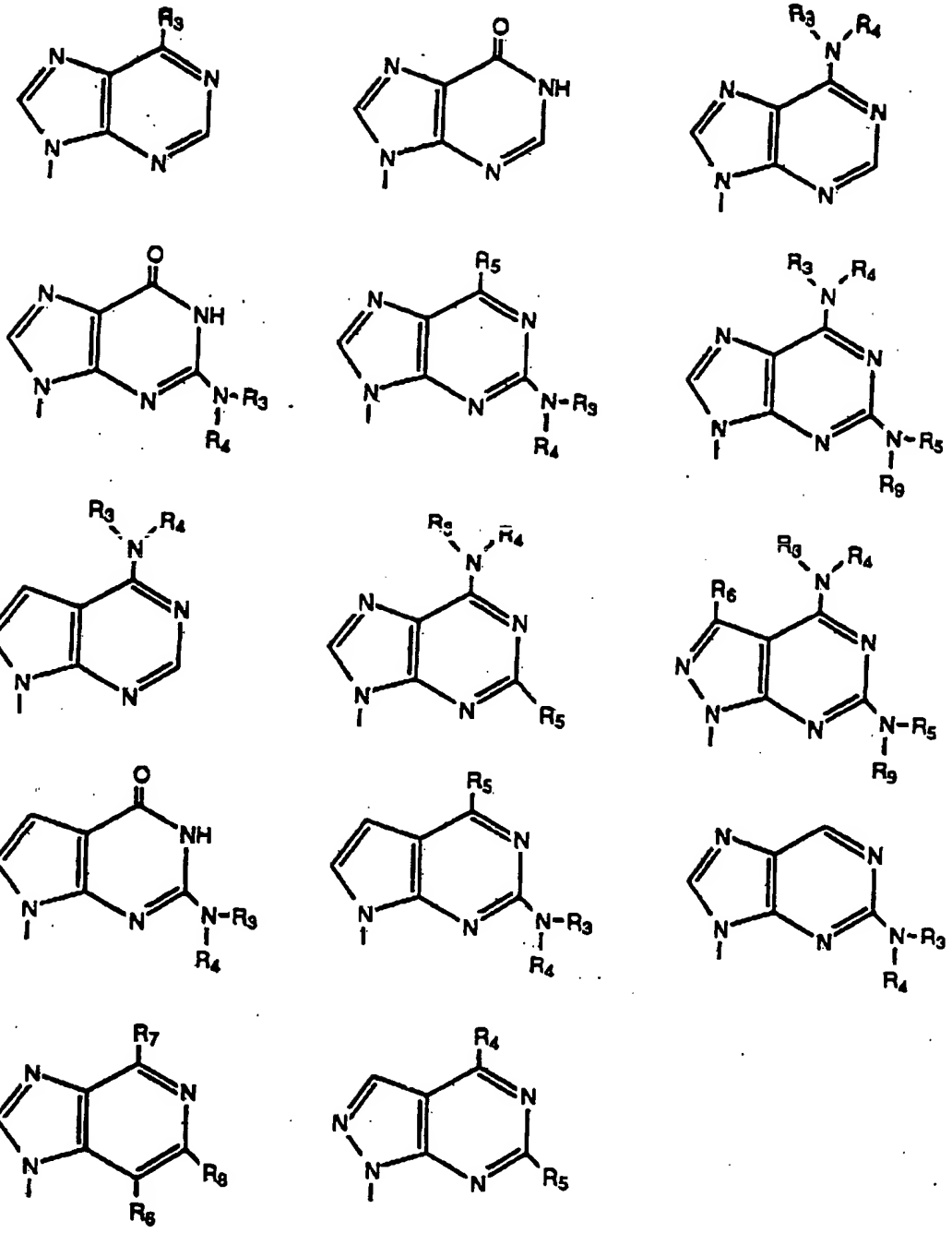


wherein R_3 is selected from the group of hydrogen, C_{1-10} acyl (e.g., acetyl), hydroxyl, substituted or unsubstituted C_{1-6} alkyl, and substituted or unsubstituted C_{1-6} alkenyl or alkynyl (e.g. propynyl);

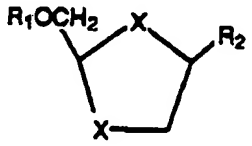
R_4 and R_5 are independently selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkenyl or alkynyl, bromine, chlorine, fluorine, iodine, and thioaryl;

R_6 is selected from the group of hydrogen, bromine, chlorine, fluorine, iodine, cyano, carboxy, carboxamide, ethoxycarbonyl, carbamoyl, and thiocarbamoyl;

R_7 and R_8 are independently selected from the group of hydrogen, bromine, chlorine, fluorine, iodine, substituted or unsubstituted amino, and hydroxy; and

R_9 is selected from the group of hydrogen, C_{1-10} acyl, hydroxyl, substituted or unsubstituted C_{1-6} alkyl, and substituted or unsubstituted C_{1-6} alkenyl or alkynyl; and pharmaceutically acceptable derivatives.

The preferred 2-substituted 4-substituted 1,3-dithiolane of this invention is a compound of formula (Ib):

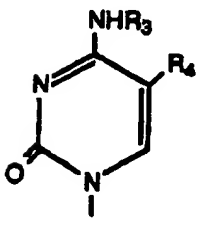


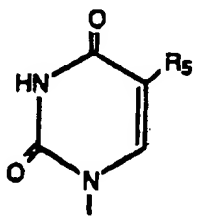
(Ib)

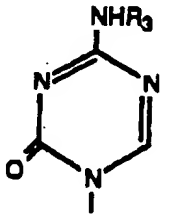
wherein each X is independently selected from the group consisting of S, S=O, and SO_2;

R_1 is hydrogen; and

preferably, R_2 is a heterocyclic radical selected from the group consisting of:







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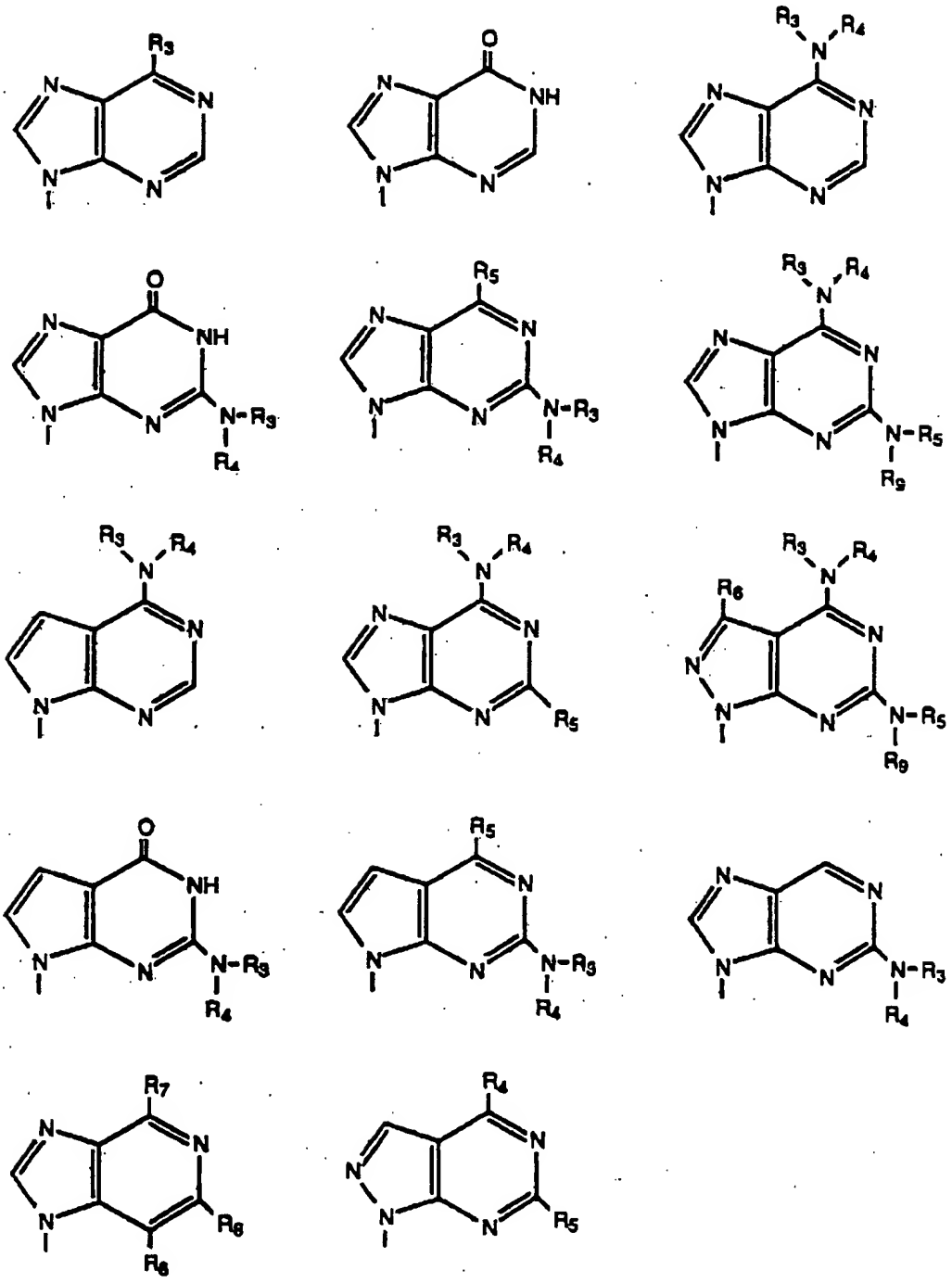


wherein R_3 is selected from the group of hydr gen, C_{1-10} acyl (e.g., acetyl), hydroxyl, substituted or unsubstituted C_{1-6} alkyl, and substituted or unsubstituted C_{1-6} alkenyl or alkynyl (e.g. propynyl);

R_4 and R_5 are independently selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkenyl or alkynyl, bromine, chlorine, fluorine, iodine, and thioaryl;

R_6 is selected from the group of hydrogen, bromine, chlorine, fluorine, iodine, cyano, carboxy, carboxamide, ethoxycarbonyl, carbamoyl, and thiocarbamoyl;

R_7 and R_8 are independently selected from the group of hydrogen, bromine, chlorine, fluorine, iodine, substituted or unsubstituted amino, and hydroxy; and

R_9 is selected from the group of hydrogen, C_{1-10} acyl, hydroxyl, substituted or unsubstituted C_{1-6} alkyl, and substituted or unsubstituted C_{1-6} alkenyl or alkynyl; and pharmaceutically acceptable derivatives.

As used herein, the term "acyl" refers to a radical derived from a carboxylic acid, substituted or unsubstituted, by replacement of the -OH group. Like the acid to which it is related, an acyl radical may be aliphatic or aromatic, substituted or unsubstituted, and whatever the structure of the rest of the molecule may be, the properties of the functional group remain essentially the same. The use of the term "aroyl" is meant to refer to acyl groups derived from aromatic acids and describes a preferred subset of the term "acyl". Other suitable acyl groups will include, for example: acetyl, propionyl, isobutanoyl, pivaloyl, hexanoyl, trifluoroacetyl, chloroacetyl, cyclohexanoyl, chlorobenzoyl, methoxybenzoyl, trifluoromethylbenzoyl, 1-naphthaloyl, 2-naphthaloyl, phenacyl, nitrobenzoyl,

α-hydroxy-α-phenylacetyl, α-methoxy-α-phenylacetyl, aminoacetyl, α-amino-β-phenylpropionyl, and α-methoxy-α-(trifluorom thyl) phenacyl.

As used herein, "a pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of formula (I) or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) a compound of formula (I) or an antivirally active metabolite or residue thereof.

Pharmaceutically acceptable salts of the compounds of formula (I) include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-(C_{1-4} alkyl)$_4^+$ salts.

References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable derivatives.

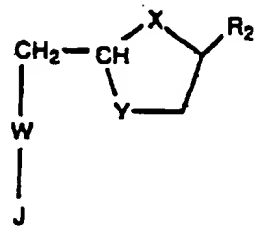
It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof, at functional groups in both the base moiety, R_2, and at the hydroxymethyl group of the oxathiolane or dithiolane ring. Modification at all such functional groups is

included within the scope of the invention. However, of particular interest are pharmaceutically acceptable derivatives (e.g., esters or esters of amino acids) obtained by modification of the 2-hydroxymethyl group of the oxathiolane or dithiolane ring.

Preferred esters of the compounds of formula (I) include the compounds in which R_1 is replaced by a carboxyl function $R-\overset{O}{\overset{\|}{C}}$ in which the non-carbonyl moiety R of the ester grouping is selected from hydrogen, straight or branched chain alkyl (e.g., methyl, ethyl, n-propyl, t-butyl, n-butyl), alkoxyalkyl (e.g., methoxymethyl), aralkyl (e.g., benzyl), aryloxyalkyl (e.g., phenoxymethyl), aryl (e.g., phenyl optionally substituted by halogen, C_{1-4} alkyl or C_{1-4} alkoxy); substituted dihydro pyridinyl (e.g., N-methyldihydro pyridinyl); sulphonate esters such as alkyl- or aralkylsulphonyl (e.g., methanesulphonyl); sulfate esters; amino acid esters (e.g., L-valyl or L-isoleucyl) and mono-, di- or tri-phosphate esters.

Also included within the scope of such esters are esters derived from polyfunctional acids such as carboxylic acids containing more than one carboxyl group, for example, dicarboxylic acids $HO_2C(CH_2)_nCO_2H$ where n is an integer of 1 to 10 (for example, succinic acid) or phosphoric acids. Methods for preparing such esters are well known. See, for example, E. Hahn et al., "Nucleotide dimers as anti-human immunodeficiency virus agents", Nucleotide Analogues As Antiviral Agents, J.C. Martin, Ed. Symposium Series #401, American Chemical Society, pp. 156-159 (1989) and M. Busso et al., "Nucleotide dimers suppress HIV expression in vitro", AIDS Research and Human Retroviruses, 4(6), pp. 449-455 (1988). Where esters are derived from such acids, each acidic group is preferably esterified by a compound of formula (I) or other nucleosides or analogues and

derivatives thereof to provide esters of the formula (IV) where:



(IV)

W is $-O-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-O-$ and n is an integer of 1 to 10 or $-O-\overset{O}{\overset{\|}{P}}(O^-)-O-$ or $-O-\overset{S}{\overset{\|}{P}}(O^-)-O-$, J is any nucleoside or nucleoside analogue or derivative thereof and X, Y, and R_2 are as defined above. Among the preferred nucleosides and nucleoside analogues are 3'-azido-2',3'-dideoxythymidine, 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, 2',3'-dideoxythymidine, 2',3'-dideoxy-2',3'-didehydrothymidine, and 2',3'-dideoxy-2',3'-didehydrocytidine and ribavirin and those nucleosides whose bases are depicted on pages 7-8 of this specification. The preferred ester of this invention is a homodimer consisting of two nucleosides of formula (I).

With regard to the above described esters, unless otherwise specified, any alkyl moiety present advantageously contains 1 to 16 carbon atoms, preferably 1 to 4 carbon atoms and could contain one or more double bonds. Any aryl moiety present in such esters advantageously comprises a phenyl group.

In particular the esters may be a C_{1-16} alkyl ester, an unsubstituted benzoyl ester or a benzoyl ester substituted by at least one halogen (bromine, chlorine, fluorine or iodine), C_{1-6} alkyl or alkenyl, saturated or unsaturated C_{1-6} alkoxy, nitro or trifluoromethyl groups.

Specific compounds of formula (I) include: cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-4-(cytosin-1'-yl)-

1,3-oxathiolane, and mixtures thereof;

cis-2-hydroxymethyl-4-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-4-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-hydroxymethyl-4-(uracil-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-4-(uracil-1'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-hydroxymethyl-4-(thymin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-4-(thymin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-hydroxymethyl-4-(6'-chloropurin-9'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-4-(6'-chloropurin-9'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-hydroxymethyl-4-(adenin-9'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-4-(adenin-9'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-hydroxymethyl-3-oxo-4-(adenin-9'-yl)-1,3-oxathiolane;

cis-2-hydroxymethyl-4-(6'-N-methylamino-purin-9'-yl)-1,3-oxathiolane;

cis-2-hydroxymethyl-4-(6'-N,N-dimethylamino-purin-9'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-4-(6'-N,N-dimethylamino-purin-9'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-hydroxymethyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-4-(2'-chloro-amino-6'-purin-9'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-hydroxymethyl-4-(2',6'-diamino-purin-9'-yl)-1,3-oxathiolane, trang-2-hydroxymethyl-4-(2',6'-diamino-purin-9'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-hydroxymethyl-4-(guanin-9'-yl)-1,3-oxathiolane;

cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-dithiolane, trans-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-dithiolane, and mixtures thereof;

cis-2-hydroxymethyl-4-(N_4'-acetyl-cytosin-1'-yl)-1,3-dithiolane, trans-2-hydroxym thyl-4-(N_4'-acetyl-cytosin-1'-yl)-1,3-dithi lane, and mixtures thereof; and pharmaceutically acceptable derivatives thereof in the form of a racemic mixture or single enantiomer.

Preferred compounds of formula (I) are cis-2-hydroxymethyl-4-(adenin-9'-yl)-1,3-oxathiolane and pharmaceutically acceptable derivatives thereof in the form of a racemic mixture or single enantiomer.

In the processes for preparing the compounds of this invention, the following definitions are used:

R_2 is a purine or pyrimidine base or an analogue or derivative thereof;

R_w is hydrogen, trisubstituted silyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted aralkyl such as benzyl or trityl, substituted or unsubstituted C_{1-16} acyl, preferably a benzoyl or a benzoyl substituted in any position by at least one halogen (bromine, chlorine, fluorine or iodine), C_{1-6} alkyl, C_{1-6} alkoxy, nitro, or trifluoromethyl group;

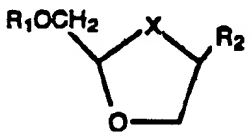
R_x is substituted or unsubstituted C_{1-6} alkyl; and

L is a "leaving group", i.e., an atom or group which is displaceable upon reaction with an appropriate base, with or without a Lewis acid. Suitable leaving groups include acyloxy groups, alkoxy groups, e.g., alkoxy carbonyl groups such as ethoxy carbonyl; halogens such as iodine, bromine, chlorine, or fluorine; amido; azido; isocyanato; substituted or unsubstituted, saturated or unsaturated thiolates, such as thiomethyl or thiophenyl; substituted or unsubstituted, saturated or unsaturated selenino compounds, such as phenyl selenide or alkyl selenide; and substituted or unsubstituted, saturated or unsaturated aliphatic or aromatic ketones such as methyl ketone.

A suitable leaving group may also be -OR, where R is a substituted or unsubstituted, saturated or unsaturated

alkyl group, e.g., C_{1-6} alkyl or alkenyl gr up; a substituted or unsubstitut d aliphatic or aromatic acyl group, e.g., a C_{1-6} aliphatic acyl group such as acetyl and an aromatic acyl group such as benzoyl; a substituted or unsubstituted, saturated or unsaturated alkoxy or aryloxy carbonyl group, such as methyl carbonate and phenyl carbonate; substituted or unsubstituted sulphonyl imidazolide; substituted or unsubstituted aliphatic or aromatic amino carbonyl group, such as phenyl carbamate; substituted or unsubstituted alkyl imidate group such as trichloroacetamidate; substituted or unsubstituted, saturated or unsaturated phosphonates, such as diethylphosphonate; substituted or unsubstituted aliphatic or aromatic sulphonyl group, such as tosylate; or hydrogen.

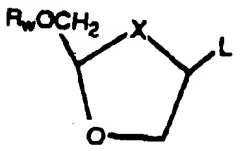
Oxathiolane compounds of formula (Ia),



(Ia)

wherein X is S, S=O, or SO_2, and their pharmaceutically acceptable derivatives, may be prepared according to the processes discussed herein or by any method known in the art for the preparation of compounds of analogous structure.

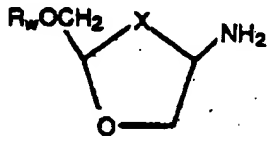
In one such process for producing oxathiolanes of this invention, a compound of formula (V),



(V)

wherein R_w is hydrogen or a hydroxyl protecting group and L is a displaceable atom or group, i.e., a leaving group, is reacted with an appropriate base.

In a second process for producing oxathiolanes of this invention, a compound of formula (VI)



(VI)

may be converted to a compound of formula (Ia) by conversion of the anomeric NH_2 group to the required base by methods well known in the art of nucleoside chemistry.

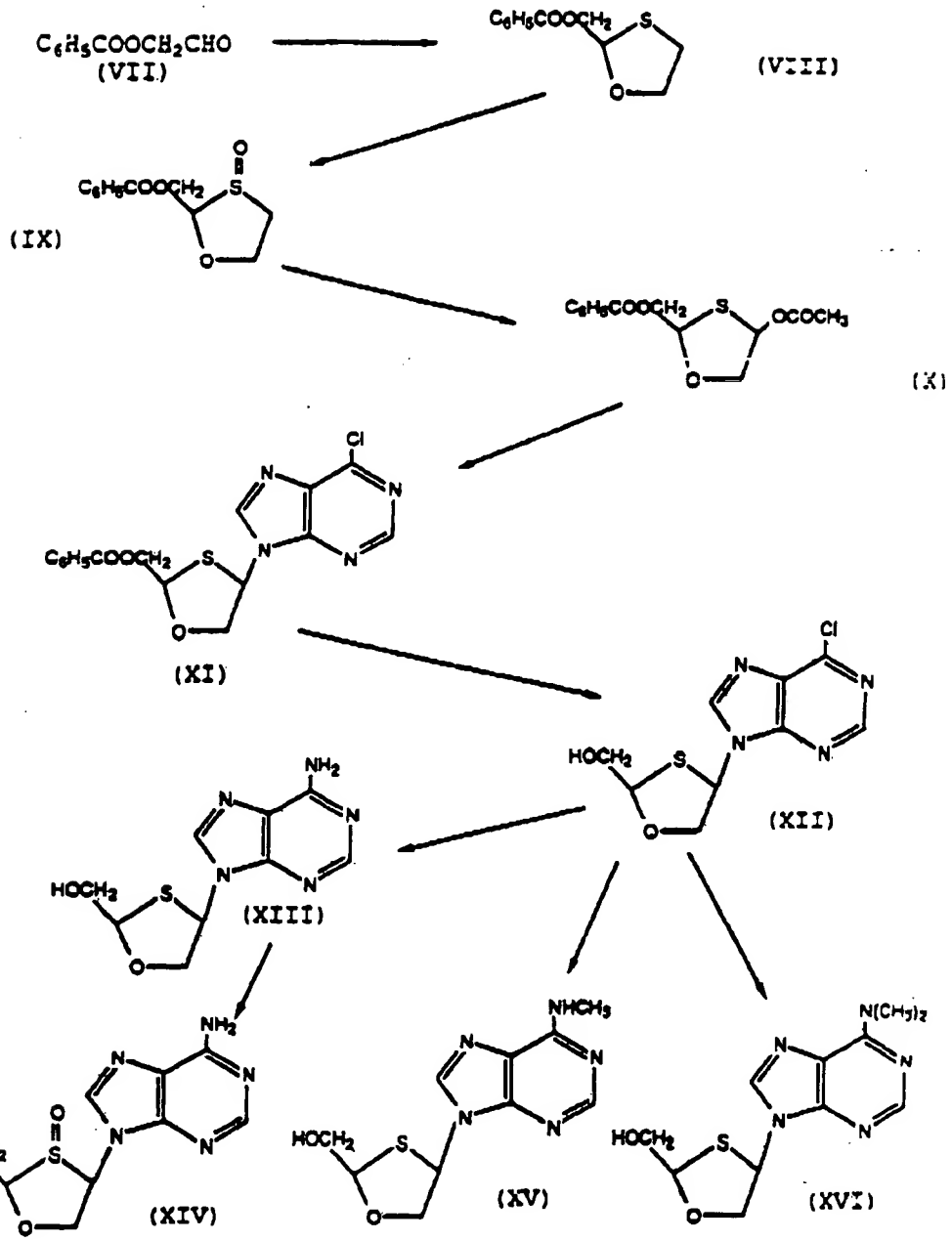
The 1,3-oxathiolanes of formula (Ia) may also be prepared, for example, by reaction of an aldehyde of formula (VII)

$$C_6H_5COOCH_2CHO \qquad \text{(VII)}$$

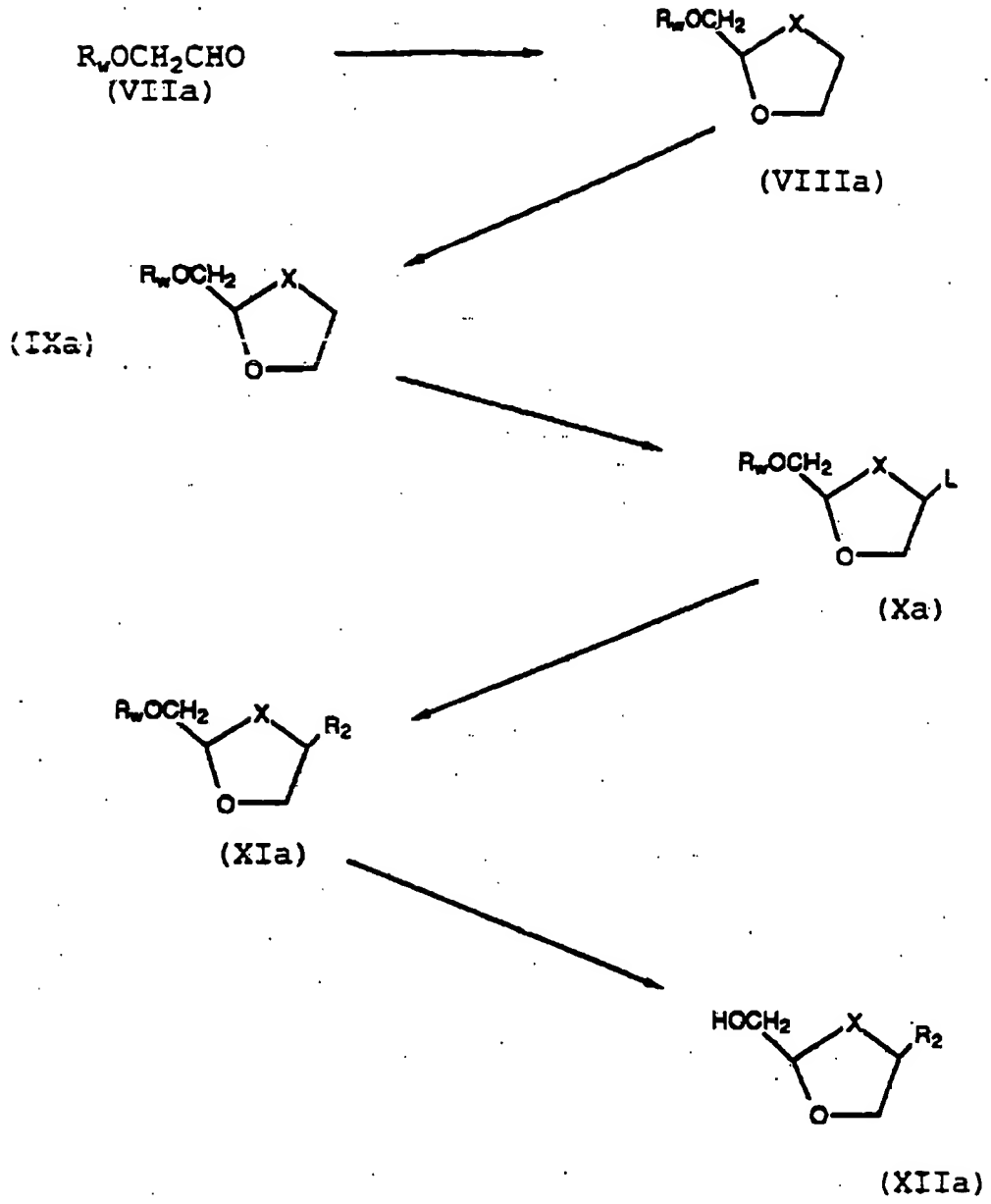
with 2-mercaptoethanol in a compatible organic solvent followed by Pummerer rearrangements as is know in the art (T. Durst, "Dimethylsulfoxide in Organic Synthesis", Adv. Org. Chem., E.C. Taylor and B. Wynberg, Eds., 6, pp. 356-365 (1969)) to give 1,3-oxathiolanes of formula (V), which are converted to 1,3-oxathiolanes of formula (Ia) by methods known in the art of nucleoside chemistry.

Another process for preparing the 1,3-oxathiolanes of formula (Ia) is illustrated in SCHEME 1. Although this process is illustrated using specific reagents and compounds, it will be appreciated by one of skill in the art that suitable analogous reactants may be used to prepare analogous products, as depicted, for example, in SCHEME 1A.

SCHEME 1



SCHEME 1A



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Th various steps involved in the synth sis of 1,3-oxathiolanes f formula (Ia) as illustrated in SCHEME 1 may be briefly described as follows:

Step 1: Benzoyloxyacetaldehyde of formula (VII) or any aldehyde of the formula R_wOCH_2CHO (C.D. Hurd and E.M. Filiachione, "A new approach to the syntheses of aldehyde sugars", J. Am. Chem. Soc., 61, pp. 1156-1159 (1939)) is condensed with a mercaptoalcohol such as 2-mercaptoethanol in a compatible organic solvent, such as toluene, containing a catalytic amount of a strong acid to give the intermediate shown in formula (VIII).

Step 2: The 1,3-oxathiolane of formula (VIII) is then oxidized with a peracid such as magnesium monoperoxyphthalic acid in a compatible organic solvent such as methylene chloride containing a salt such as tetrabutyl ammonium bromide to give the sulfoxide intermediate shown in formula (IX).

Step 3: The sulfoxide intermediate shown in formula (IX) is treated with an acid anhydride such as acetic anhydride or any other anhydride of the formula $(R_x)_2O$ in the presence of a buffer such as tetra-n-butylammonium acetate to give the 2,4-disubstituted-1,3-oxathiolane of formula (X) (T. Durst, Adv. Org. Chem., 6, pp. 356-365 (1969)).

Step 4: The 1,3-oxathiolane of formula (X) is then reacted with a pyrimidine or purine base or analogue thereof, (e.g., 6-chloropurine) previously silylated with, for example, hexamethyldisilazane in a compatible solvent using a Lewis acid or trimethylsilyl triflate to give the intermediate of formula (XI) as cis and trans isomers. The isomers may be separated, preferably by chromatography, to give pure cis (XI) and pure trans (XI).

Step 5: The benzoate function of the compound of formula (XI) (cis or trans isomer), is hydrolyzed

using a base such as methanolic amm nia to obtain the compound shown in formula (XII) as cis- or trans- isomer.

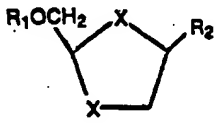
Step 6: The chloro function of product of formula (XII) is displaced by methanolic ammonia preferably under pressure to give the product shown in formula (XIII) as a cis- or trans- isomer.

Step 7: The preceding isomers of formula (XIII) are treated with an oxidizing agent, e.g., a suitable peracid, in a compatible organic solvent to give the 3-oxide (sulfoxide) of formula (XIV).

Step 8: The chloro function of the compound of formula (XII) is displaced by ethanolic methylamine, preferably under pressure, to give the product shown in formula (XV) as a cis- or trans- isomer.

Step 9: The chloro function of the compound of formula (XII) is displaced by ethanolic dimethylamine, preferably under pressure, to give the product shown in formula (XVI) as a cis- or trans- isomer.

Dithiolane compounds of formula (Ib),



(Ib)

wherein each X is independently selected from S, S=O, or SO_2, and their pharmacologically acceptable derivatives, may be prepared according to the processes discussed herein or by any method known in the art for the preparation of compounds of analogous structure.

In one such process for preparing the dithiolanes of this invention, a compound of formula (XVII)

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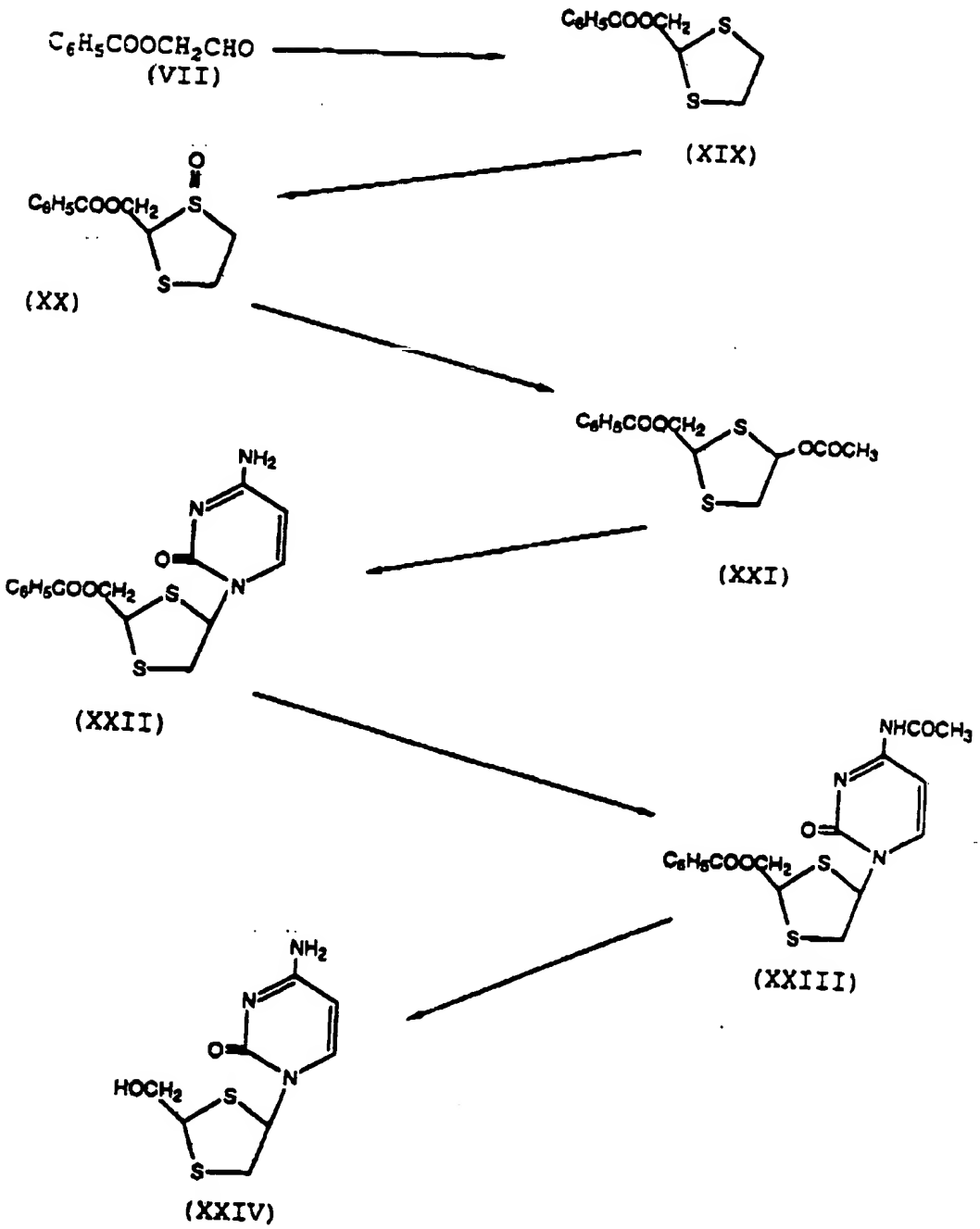
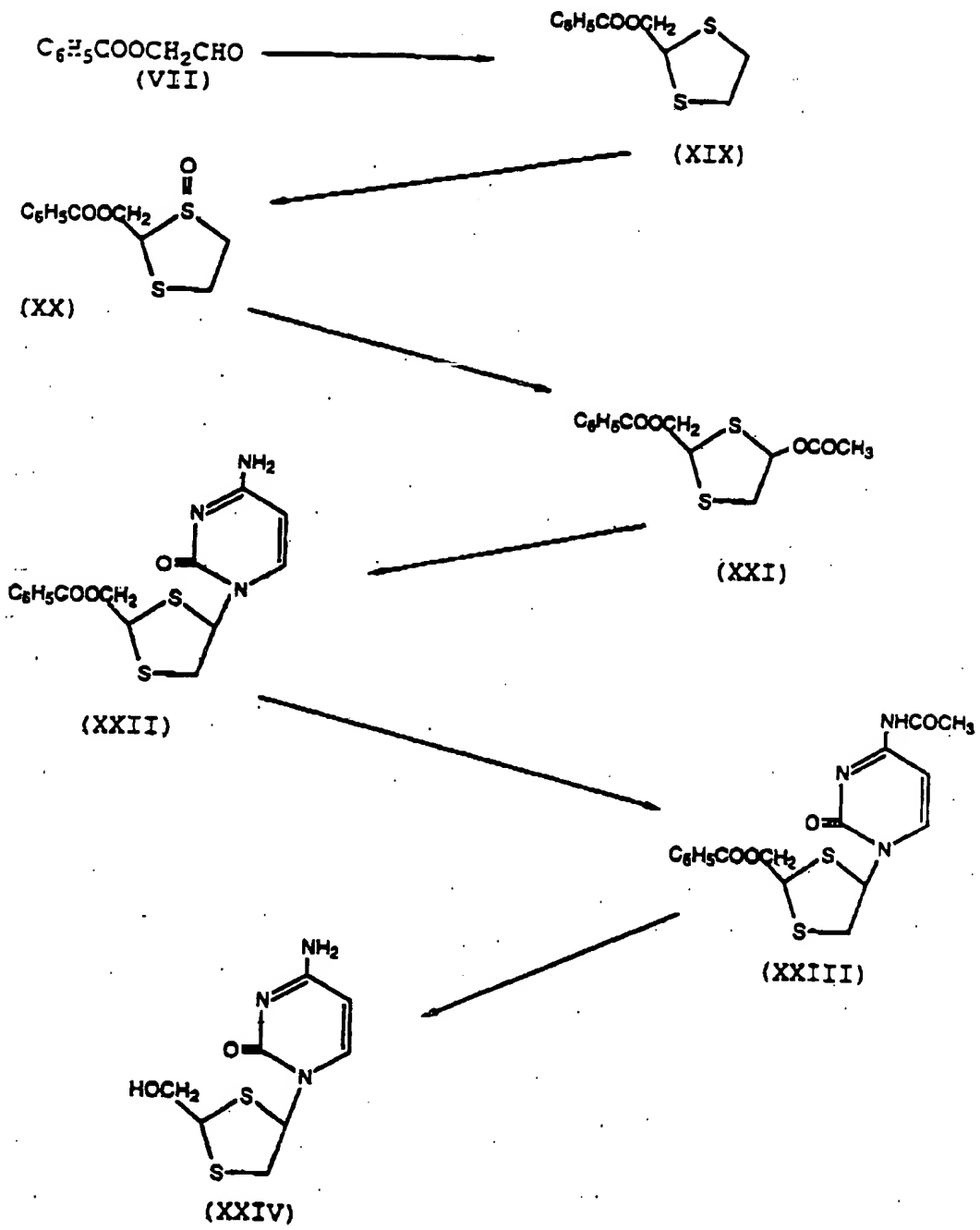
SCHEME 2



SCHEME 2A



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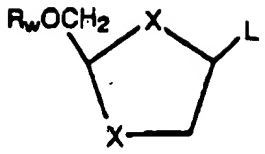
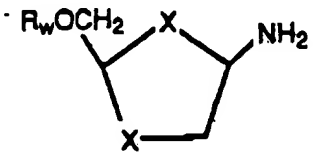


(XVII)

wherein R_w is hydrogen or hydroxyl protecting group and L is a displaceable atom or group, i.e., a leaving group, is reacted with an appropriate base.

In another process for preparing the dithiolanes of this invention, a compound of formula (XVIII)



(XVIII)

may be converted to a compound of formula (Ib) by conversion of the anomeric NH_2 group to the required base by methods well known in the art of nucleoside chemistry.

The 1,3-dithiolanes of formula (Ib) may also be prepared, for example, by reaction of an aldehyde of formula (VII)

$$C_6H_5COOCH_2CHO \qquad \text{(VII)}$$

with 1,2-ethanedithiol in a compatible organic solvent followed by Pummerer rearrangement as is known in the art (T. Durst, Adv. Org. Chem., 6, p. 356-365 (1969)) to give 1,3-dithiolanes of formula (XVII) which are converted to 1,3-dithiolanes of formula (Ib) by methods known in the art of nucleoside chemistry.

Another process for preparing the 1,3-dithiolanes of formula (Ib) is illustrated in SCHEME 2. Although this process is illustrated using specific

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The various steps involved in the synthesis of 1,3-dithiolanes of formula (Ib) as illustrated in SCHEME 2 may be briefly described as follows:

Step 1: Benzoyloxyacetaldehyde of formula (VII) or any aldehyde of the formula R_wOCH_2CHO (C.D. Hurd and E.M. Filiachione, "A new approach to the synthesis of aldehyd sugars", J. Am. Chem. Soc., 61, pp. 1156-1159 (1939)) is condensed with a vicinal dithiol such as 1,2-thanedithiol in a compatible organic solvent, such as toluene, containing a catalytic amount of a strong acid to give the intermediate shown in formula (XIX).

toluene, containing a catalytic amount of a strong acid to give the intermediate shown in f rmula (XIX).

Step 2: Th 1,3-dithiolan of formula (XIX) is then oxidiz d with a peracid, such as m-chloroperbenzoic acid in a compatible organic solvent, such as methylene chloride to give the sulfoxide intermediate sh wn in formula (XX).

Step 3: The sulfoxide intermediate shown in formula (XX) is treated with an acid anhydride, such as acetic anhydride or any other anhydride of the formula $(R_x)_2O$, in the presence of a base, such as sodium acetate, to give the 2,4-disubstituted-1,3-dithiolane of formula (XXI) (T. Durst, Adv. Org. Chem., 6, pp. 356-365 (1969)).

Step 4: The 1,3-dithiolane of formula (XXI) is then reacted with a pyrimidine or purine base or analogue thereofcontaining an NH_2 group (e.g., cytosine) previously silylated with, for example, hexamethyl-disilazane, in a compatible solvent using a Lewis acid, such a tin IV tetrachloride or trimethylsilyl triflate, to give the intermediate of formula (XXII) as cis and trans isomers.

Step 5: The amine function of the compound shown in formula (XXII) is acetylated with acetic anhydride to yield the intermediate of formula (XXIII) as cis and trans isomers which are separated, preferably by

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chromatography, to give pure cis (XXIII) and pure trans (XXIII).

Step 6: The cis and trans isomers of formula (XXIII) are treated with methanolic ammonia to obtain the desired product shown in formula (XXIV) as a cis or trans isomer.

Another process for preparing the compounds of formula (Ib) is illustrated in SCHEME 3. Although this process is illustrated using specific reagents and compounds, it will be appreciated by one of skill in the art that suitable analogous reactants may be used to prepare analogous products, as depicted, for example, in SCHEME 3A.

reagents and compounds, it will be appreciated by one of skill in the art that suitable analogous reactants may be used to prepare analogous products, as depicted, for example, in SCHEME 2A.

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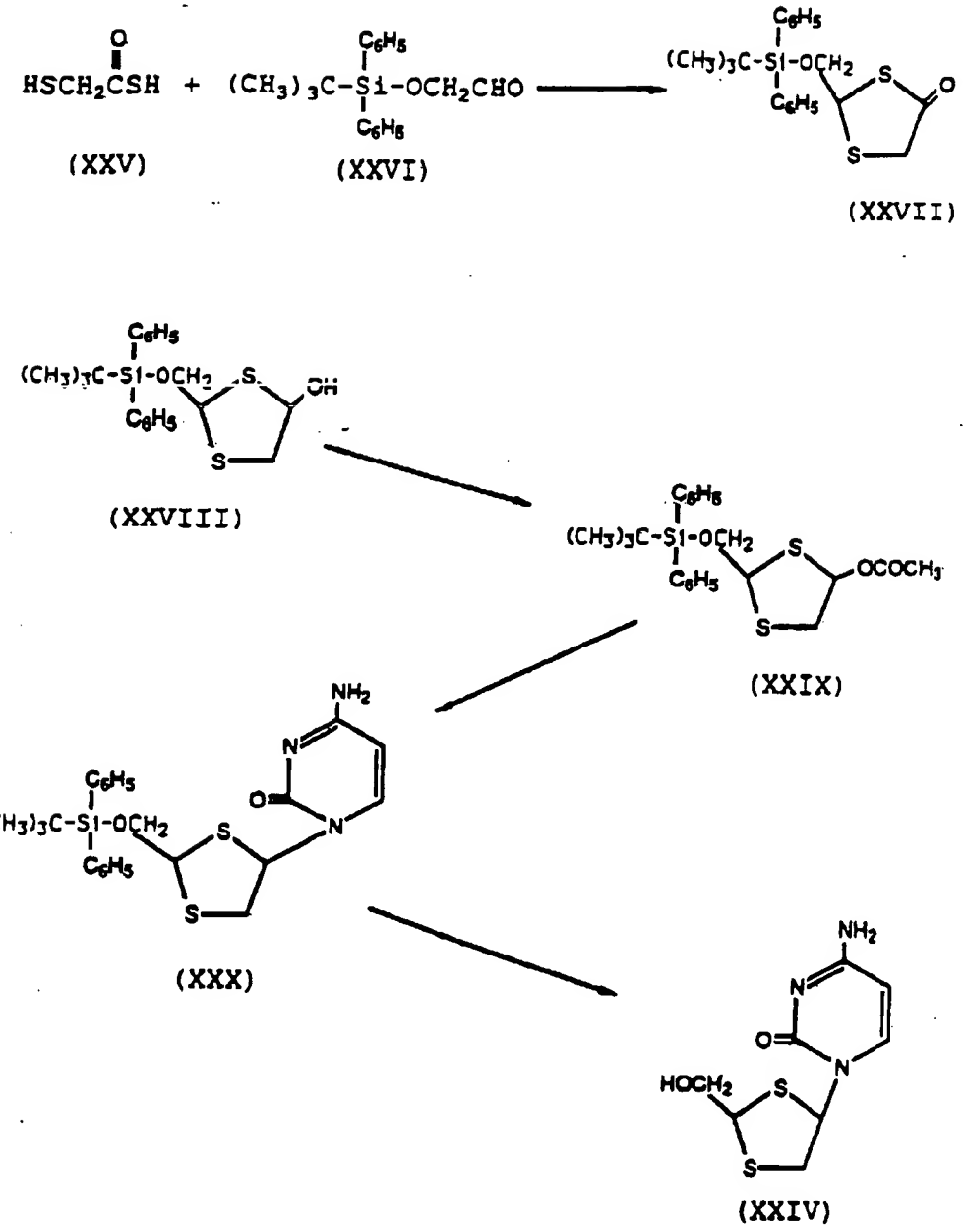
SCHEME 3



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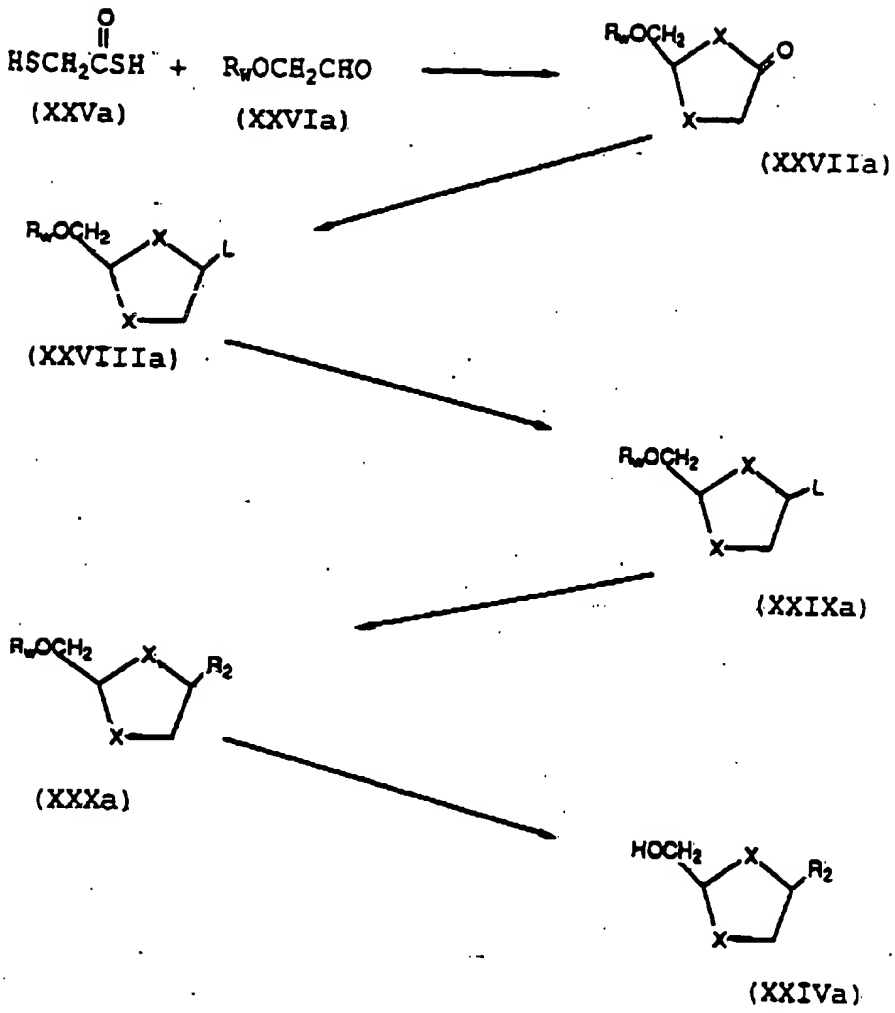
SCHEME 3A


HSCH2CSH
(XXVa)
RwOCH2CHO
(XXVIa)
RwOCH2
X
O
(XXVIIa)
L
(XXVIIIa)
(XXIXa)
R2
(XXXa)
HOCH2
(XXIVa)

The various steps involved in the synthesis of 1,3-dithiolanes of formula (Ib) as illustrated in SCHEME 3 may be briefly described as follows:

Step 1: The known mercaptothioacetic acid of formula (XXV) (S. Satsumahyashi et al., "The Synthesis of 1,3-Dithiolanone Derivatives", J. Org. Chem., 38, pp. 3953-3954 (1973) is reacted with an appropriate aldehyde of formula R_wOCH_2CHO, wherein R_w is preferably a silyl protecting group and more preferably, R_w is a t-butyldiphenylsilyl protecting group, in a compatible solvent, in the presence of an appropriate Lewis acid such as zinc iodide to give the intermediate of formula (XXVII).

Step 2: The compound of formula (XXVII) is reduced with an appropriate reducing agent such as diisobutylaluminum hydride in a compatible organic solvent such as toluene to give the compound of formula (XXVIII).

Step 3: The compound of formula (XXVIII) is reacted with an acid anhydride or acid chloride such as acetic anhydride in the presence of pyridine and an acylation catalyst such as dimethylaminopyridine to give the compound of formula (XXIX).

Step 4: The 1,3-dithiolane of formula (XXIX) is then reacted with a pyrimidine or purine base (e.g., cytosine) or analogue thereof previously silylated with, for example, hexamethyldisilazane in a compatible organic solvent using a Lewis acid, such as tin IV tetrachloride to give the intermediate of formula (XXX) as cis and trans isomers.

Step 5: The cis and trans isomers of formula (XXX) are treated with tetra n-butylammonium fluoride or other desilylating agents in an appropriate organic solvent such as tetrahydrofuran to give the desired product (XXIV) as a cis and trans isomers.

The cis and trans isomers of formula (XXIV) ar separated preferably by high pressure liquid chromatography to obtain the desired 1,3-dithiolane of formula (Ib) as a pure cis or trans isomer.

Many of the reactions in the above-described processes have been extensively reported in the context of purine nucleoside synthesis, for example, in L.B. Townsend, "Chemistry of the heterocyclic moiety of purine nucleosides and some closely related analogues", Nucleoside Analogues - Chemistry, Biology, and Medical Applications, R.T. Walker et al., Eds., Plenum Press, New York (1979) at pages 193-223, the text of which is incorporated by reference herein.

It will be appreciated that the reactions of the above-described processes may require the use of, or conveniently may be applied to, starting materials having protected functional groups, and deprotection might thus be required as an intermediate or final step to yield the desired compound. Protection and deprotection of functional groups may be effected using conventional means. Thus, for example, amino groups may be protected by a group selected from aralkyl (e.g., benzyl), acyl or aryl (e.g., 2,4-dinitrophenyl); subsequent removal of the protecting group being effected when desired by hydrolysis or hydrogenolysis as appropriate using standard conditions. Hydroxyl groups may be protected using any conventional hydroxyl protecting group, for example, as described in "Protective Groups in Organic Chemistry", Ed. J.F.W. McOmie (Plenum Press, 1973) or "Protective Groups in Organic Synthesis" by Theodora W. Greene (John Wiley and Sons, 1981). Examples of suitable hydroxyl protecting groups include groups selected from alkyl (e.g., methyl, t-butyl or methoxymethyl), aralkyl (e.g., benzyl, diphenylmethyl or triphenylmethyl), heterocyclic groups such as tetrahydropyranyl, acyl, (e.g., acetyl or benzoyl) and silyl groups such as

trialkylsilyl (e.g., t-butyldimethylsilyl). The hydroxyl protecting groups may be removed by conventional techniques. Thus, for example, alkyl, silyl, acyl and heterocyclic groups may be removed by solvolysis, e.g., by hydrolysis under acidic or basic conditions. Aralkyl groups such as triphenylmethyl may similarly be removed by solvolysis, e.g., by hydrolysis under acidic conditions. Aralkyl groups such as benzyl may be cleaved, for example, by treatment with BF_3/etherate and acetic anhydride followed by removal of acetate groups so formed at an appropriate stage in the synthesis. Silyl groups may also conveniently be removed using a source of fluoride ions such as tetra-n-butylammonium fluoride.

In the above-described processes, the compounds of formula (I) are generally obtained as a mixture of the cis and trans isomers.

These isomers may be separated, for example, by acetylation, e.g., with acetic anhydride followed by separation by physical means, e.g., chromatography on silica gel and deacetylation, e.g., with methanolic ammonia or by fractional crystallization.

Pharmaceutically acceptable salts of the compounds of the invention may be prepared as described in United States Patent No. 4,383,114, the disclosure of which is incorporated by reference herein. Thus, for example, when it is desired to prepare an acid addition salt of a compound of formula (I), the product of any of the above procedures may be converted into a salt by treatment of the resulting free base with a suitable acid using conventional methods. Pharmaceutically acceptable acid addition salts may be prepared by reacting the free base with an appropriate acid optionally in the presence of a suitable solvent such as an ester (e.g., ethyl acetate) or an alcohol (e.g., methanol, ethanol or isopropanol). Inorganic basic salts may be prepared by reacting the free base with a suitable base such as an

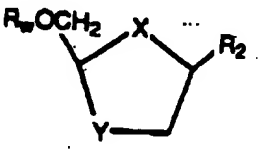
alkoxide (e.g., sodium methoxide) optionally in the presence of a solvent such as an alcohol (e.g., methanol). Pharmaceutically acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compounds of formula (I) using conventional methods.

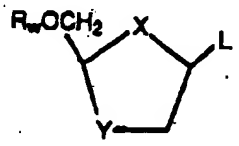
A compound of formula (I) may be converted into a pharmaceutically acceptable phosphate or other ester by reaction with a phosphorylating agent, such as $POCl_3$, or a suitable esterifying agent, such as an acid halide or anhydride, as appropriate. An ester or salt of a compound of formula (I) may be converted to the parent compound, for example, by hydrolysis.

Where the compound of formula (I) is desired as a single isomer it may be obtained either by resolution of the final product or by stereospecific synthesis from isometrically pure starting material or any convenient intermediate.

Resolution of the final product, or an intermediate or starting material therefore may be effected by any suitable method known in the art: see for example, Stereochemistry of Carbon Compounds, by E.L. Eliel (McGraw Hill, 1962) and Tables of Resolving Agents, by S.H. Wilen.

The intermediates of formulas (Ic) and (Id) are useful in the above-described processes for making the oxathiolane and dithiolane compounds of this invention

(Ic) 

 (Id)

wherein R_w is trisubstituted silyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted

aralkyl such as benzyl or trityl, substituted or unsubstituted C_{1-16} acyl, preferably a benzoyl or a benzoyl substituted in any position by at least one halogen (bromine, chlorine, fluorine or iodine), C_{1-6} alkyl, C_{1-6} alkoxy, nitro, or trifluoromethyl group; and

R_2 is a purine or pyrimidine base or an analogue or derivative thereof; and

L is a leaving group as previously defined.

The following intermediates of formula (Ic) are of particular importance:

cis-2-benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-benzoyloxymethyl-4-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-4-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-benzoyloxymethyl-4-(uracil-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-4-(uracil-1'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-benzoyloxymethyl-4-(thymin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-4-(thymin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-benzoyloxymethyl-4-(6'-chloropurin-9'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-4-(6'-chloropurin-9'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-benzoyloxymethyl-4-(adenin-9'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-4-(adenin-9'-yl)-1,3-oxathiolane;

cis-2-benzoyloxymethyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-dithiolane, trans-2-benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-dithiolane, and mixtures thereof;

cis-2-benzoyloxymethyl-4-(N_4'-acetyl-cytosin-1'-yl)-1,3-dithiolan , trans-2-benzoyloxymethyl-4-(N_4'-acetyl-cytosin-1'-yl)-1,3-dithiolane, and mixtures thereof;

cis-2-t-butyldiphenylsilyloxymethyl-4-(cytosin-1'-yl)-1,3-dithiolane, trans-2-t-butyldiphenylsilyloxymethyl-4-(cytosin-1'-yl)-1,3-dithiolane, and mixtures thereof; and

cis-2-t-butyldiphenylsilyloxymethyl-4-(N_4'-acetoxy-cytosin-1'-yl)-1,3-dithiolane, trans-2-t-butyldiphenylsilyloxymethyl-4-(N_4'-acetoxy-cytosin-1'-yl)-1,3-dithiolane, and mixtures thereof.

The following intermediates of formula (Id) are of particular importance:

2-benzoyloxymethyl-1,3-oxathiolane;

cis-2-benzoyloxymethyl-1-oxo-1,3-oxathiolane, trans-2-benzoyloxymethyl-1-oxo-1,3-oxathiolane, and mixtures thereof;

cis-2-benzoyloxymethyl-4-acetoxy-1,3-oxathiolane, trans-2-benzoyloxymethyl-4-acetoxy-1,3-oxathiolane, and mixtures thereof;

2-t-butyldiphenylsilyloxymethyl-1,3-dithiolane;

2-benzoyloxymethyl-1,3-dithiolane;

cis-2-benzoyloxymethyl-3-oxo-1,3-dithiolane, trans-2-benzoyloxymethyl-3-oxo-1,3-dithiolane, and mixtures thereof;

cis-2-benzoyloxymethyl-4-acetoxy-1,3-dithiolane, trans-2-benzoyloxymethyl-4-acetoxy-1,3-dithiolane, and mixtures thereof;

cis-2-t-butyldiphenylsilyloxymethyl-4-hydroxy-1,3-dithiolane, trans-2-t-butyldiphenylsilyloxymethyl-4-hydroxy-1,3-dithiolane, and mixtures thereof; and

cis-2-t-butyldiphenylsilyloxymethyl-4-acetoxy-1,3-dithiolane, trans-2-t-butyldiphenylsilyloxymethyl-4-acetoxy-1,3-dithiolane, and mixtures thereof.

The compounds of the invention either themselves p ss ss antiviral activity and/or are

metabolizable to such compounds. In particular these compounds ar effective in inhibiting the replication of hepatitis B virus and retroviruses, including human retroviruses such as human immunodeficiency viruses (HIV's), the causative agents of AIDS.

There is thus provided as a further aspect of the invention a compound formula (I) or a pharmaceutically acceptable derivative thereof for use as an active therapeutic agent in particular as an antiviral agent, for example in the treatment of hepatitis B viral and retroviral infections.

In a further or alternative aspect there is provided a method for the treatment of a viral infection, in particular an infection caused by hepatitis B virus or a retrovirus such as HIV, in a mammal, including man, comprising administration of an effective amount of an antiviral compound of formula (I) or a pharmaceutically acceptable derivative thereof.

There is also provided in a further or alternative aspect of this invention, use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a viral infection.

The compounds of the invention are also useful in the treatment of AIDS-related conditions such as AIDS-related complex (ARC), persistent generalized lymphadenopathy (PGL), AIDS-related neurological conditions (such as dementia), anti-HIV antibody-positive and HIV-positive conditions, Kaposi's sarcoma, thrombocytopenia purpura and opportunistic infections.

The compounds of the invention are also useful in the prevention or progression to clinical illness of individuals who are anti-HIV antibody or HIV-antigen positive and in prophylaxis following exposure to HIV.

The c mpounds of formula (I) or the pahrmaceutically acceptabl derivatives thereof, may also

be used for the prevention of viral contamination of biological fluids such as blood or semen in vitro.

Certain of the compounds of formula (I) are also useful as intermediates in the preparation of other compounds of the invention.

It will be appreciated by those skilled in the art that references herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms.

It will be further appreciated that the amount of a compound of the invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general, however, a suitable dose will be in the range from about 1 to about 750 mg/kg of body weight per day, such as 3 to about 120 mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90 mg/kg/day, most preferably in the range of 15 to 60 mg/kg/day.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

The compound is conveniently administered in unit dosage form; for example containing 10 to 1500 mg, conveniently 20 to 1000 mg, most conveniently 50 to 700 mg of active ingredient per unit dosage form.

Ideally the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 1 to 75 μM, preferably about 2 to 50 μM, most preferably about 3 to about 30 μM. This may be achieved, for example, by the intravenous injection of a 0.1 to 5% solution of the active

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ingredient, optionally in saline, or administered as a bolus containing about 0.1 to about 110 mg/kg of the active ingredient. Desirable blood levels may be maintained by a continuous infusion to provide about 0.01 to about 5.0 mg/kg/hour or by intermittent infusions containing about 0.4 to about 15 mg/kg of the active ingredient.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with one or more pharmaceutically acceptable carriers thereof and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations suitable for oral administration may conveniently be presented as discrete units such as capsules, cach ts or tablets each

containing a predetermined amount of the active ingredient; as a powder or granul s; as a solution; as a suspension; or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils) or preservatives.

The compounds according to the invention may also be formulated for parenteral administration (e.g., by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

For topical administration to the epidermis, the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling

ag nts. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavored based, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutically formulations suitable for rectal administration wherein the carrier is a solid, are most preferably represented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in molds.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient, such carriers as are known in the art to be appropriate.

For intra-nasal administration the compounds of the invention may be used as a liquid spray or dispersible powder or in the form of drops.

Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilizing agents or suspending agents. Liquid sprays are conveniently delivered from pressurized packs.

For administration by inhalation, the compounds according to the invention are conveniently delivered from an insufflator, nebulizer or a pressurized pack or other convenient means of delivering an aerosol spray.

Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges or, e.g., gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

When desired, the above described formulations adapted to give sustained release of the active ingredient, may be employed.

The pharmaceutical compositions according to the invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

The compounds of the invention may also be used in combination with other therapeutic agents, for example, other anti-infective agents. In particular the compounds of the invention may be employed together with known antiviral agents.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a physiologically acceptable derivative thereof together with another therapeutically active agent, in particular, an antiviral agent.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above

together with a pharmaceutically acceptable carrier th reof compris a further aspect of th invention.

Suitable therapeutic agents for use in such combinations include acyclic nucleosides such as acyclovir, ganciclovir, interferons such as alpha-, beta- and gamma-interferon; glucuronation inhibitors such as probenecid; nucleoside transport inhibitors such as dipyridamole; nucleoside analogues such as 3'-azido-2',3'-dideoxythymidine, 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, 2',3'-dideoxythymidine, 2',3'-dideoxy-2',3'-didehydro-thymidine, and 2',3'-dideoxy-2',3'-didehydrocytidine and ribavirin; immunomodulators such as interleukin II (IL2) and granulocyte macrophage colony stimulating factor (GM-CSF), erythropoietin, ampligen, thymomodulin, thymopentin, foscarnet, glycosylation inhibitors such as 2-deoxy-D-glucose, castanospermine, 1-deoxynojirimycin; and inhibitors of HIV binding to CD4 receptors such as soluble CD4, CD4 fragments and CD4-hybrid molecules.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When the compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same virus, the dose of each compound may be either the same or differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

The invention will be further described by the following examples which are not intended to limit the invention in any way. All temperatures are in degrees celsius.

EXAMPLES

Example 1
Benzoyloxyacetaldehyde

$$C_6H_5COOCH_2CHO \qquad \text{(VII)}$$

This known intermediate was prepared by portionwise addition of $NaIO_4$ (80 g) to a mixture of 1-benzoyl glycerol (50 g), CH_2Cl_2 (500 ml), and H_2O (25 ml) under vigorous stirring at room temperature. The resulting solution was stirred for 2 hours $MgSO_4$ (100 g) added, and the solution stirred for an additional 30 minutes. The mixture was filtered, the filtrate evaporated in vacuo and the residue distilled in vacuo to yield 26 g of pure product.

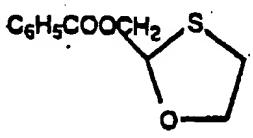
b.p. 92-94°/0.25 mm

^1H NMR (200 MH_2; TMS as internal reference):

δ(ppm in $CDCl_3$)

9.71 (s, 1H; -CHO)
8.11 (d, 2H; aromatic)
7.60 (m, 1H; aromatic)
7.46 (m, 2H; aromatic)
4.88 (s, 2H; $-CH_2CHO$)

Example 2
2-Benzoyloxymethyl-1,3-oxathiolane



(VIII)

A mixture of benzoyloxyacetaldehyde (6.21 g), 2-mercaptoethanol (3 ml) and para-toluene sulfonic acid

(0.2 g) in toluene (150 ml) was heated for 3 h urs at refluxing under water removal conditions using a Dean Stark apparatus. The mixture was cooled to room temperature, washed first with aqueous $NaHCO_3$-solution (1 x 50 ml), and then with water (2.5 ml) and dried over $MgSO_4$. The solution was filtered and the filtrate evaporated under reduced pressure. The residue was purified on silica gel using hexane:ethyl acetate (9:1) as eluant. It yielded 7.63 g (90%) of pure product, which was identified by ^1H- and ^{13}C-NMR.

R_f: 0.39 (hexane:ethyl acetate)

^1H-NMR: δ(ppm in $CDCl_3$)

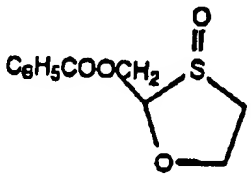
8.03 (m, 2H, aromatic)
7.53 (m, 1H, aromatic)
7.39 (m, 2H, aromatic)
5.41 (dd, 1H, C_2-H)
4.43 (m, 2H, C_2-$CH_2OCC_6H_5$)
4.21 (m, 1H, C_5-H)
3.96 (m, 1H, C_5-H)
2.98 (m, 2H, C_4-H)

^{13}C-NMR: δ(ppm in $CDCl_3$)

166.82, 133.74, 130.35, 128.97, 83.58, 71.87, 66.62 and 32.74

Example 3

2-Benzoyloxymethyl-3-oxo-1,3-oxathiolane



(IX)

Monoperoxyphthalic acid, magnesium salt (MMPP, 28 g) was added portion wise under vigorous stirring to a

mixture of 2-benzoyloxymethyl-1,3-oxathiolan (20 g), tetrabutyl amm nium bromide (0.4 g) in methylene chloride (200 ml), and water (200 ml). The mixture was stirred at room temperature for 30 minutes and the organic layer was collected. The aqueous phase was extracted with methylene chloride (3 x 75 ml) and the combined organic layer was washed first with water (2 x 100 ml), then with brine solution (100 ml), dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo and the residue was purified by chromatography on silica gel using ethyl acetate as eluant to give 18.5 g (86%) of pure product as a mixture of cis- and trans- isomers in a ratio of 1:2.

m.p.: 70-72°

^{1}H-NMR: δ(ppm in $CDCl_3$)

8.05 (m, 2H, aromatic, cis-isomer)
7.95 (m, 2H, aromatic, trans-isomer)
7.56 (m, aromatic)
7.23 (m, aromatic)
4.77 (m, 4H, C_2-H, C_5-H, and C_2-$CH_2OOCC_6H_5$)
4.43 (m, 1H, C_5-H, trans-isomer)
4.09 (m, 1H, C_5-H, cis-isomer)
3.11 (m, 2H, C_4-H, trans-isomer)
2.75 (m, 2H, C_4-H, cis-isomer)

^{13}C-NMR: δ(ppm in $CDCl_3$)

cis-isomer:

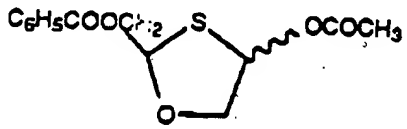
166.64, 134.02, 130.42, 129.88, 129.06, 96.16, 68.83, 59.47 and 54.30

trans-isomer:

166.36, 134.12, 130.29, 129.68, 129.15, 108.07, 70.09, 61.83 and 53.47

Example 4

2-Benzoyloxymethyl-4-acetoxy-1,3-oxathi lane



(X)

A mixture of 2-benzoyloxymethyl-3-oxo-1,3-oxathiolane (10.5 g), tetra-n-butylammonium acetate (17 g) in acetic anhydride (250 ml) was heated at 110°-120°C under argon for 14 hours and cooled to room temperature. Excess acetic anhydride was removed under reduced pressure. The residue was dissolved in methylene chloride (500 ml), washed first with saturated aqueous $NaHCO_3$ (2 x 200 ml), then with brine solution (200 ml), dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was purified by chromatography on silica gel using hexane:ethyl acetate (8:1) as eluant to give 7.4 g (60% yield) of the desired product as a mixture of cis- and trans- isomers. A small quantity of each isomer was also isolated and characterized by ^1H- and ^{13}C-NMR.

cis-isomer:

R_f: 0.43 (hexane:EtOAc)

^1H-NMR: δ(ppm in $CDCl_3$)

8.05 (m, 2H, aromatic)
7.58 (m, 1H, aromatic)
7.45 (m, 2H, aromatic)
6.24 (d, 1H, C_4-H)
5.50 (t, 1H, C_2-H)
4.61 (d, 1H, C_2-$CH_2OOCC_6H_5$)
4.53 (d, 2H, C_5-H)
3.94 (dd, 1H, C_5-H)
2.05 (s, 3H, CH_3)

trans-isomer:

R_f: 0.43 (hexane:EtOAc 7:3)

^{1}H-NMR: δ(ppm in $CDCl_3$)

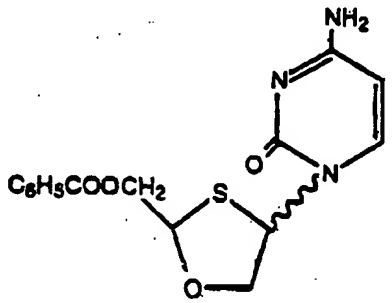
8.04 (m, 2H, aromatic)
7.58 (m, 1H, aromatic)
7.45 (m, 2H, aromatic)
6.27 (dd, 1H, C_4-H)
5.73 (dd, 1H, C_2-H)
4.53 (dd, 1H, C_2-$CH_2OOCC_6H_5$)
4.34 (dd, 1H, C_5-H)
4.26 (dd, 1H, C_2-$CH_2OCC_6H_5$)
4.20 (dd, 1H, C_5-H)
2.09 (s, 3H, CH_3)

^{13}C-NMR: δ(ppm in $CDCl_3$)

177.66, 166.37, 133.46, 129.93, 128.60, 83.76, 81.22, 74.33, 64.65 and 20.79

Example 5

Cis- and trans-2-benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane



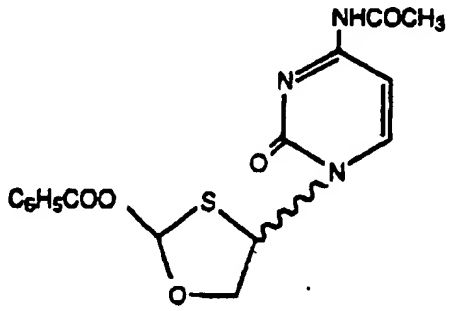
(XXXI)

A mixture of cytosine (206 mg), ammonium sulfate (10 mg) and hexamethyldisilazane (HMDS, 10 ml) was heated at refluxing under argon until a clear solution resulted. Excess reagents were evaporated in vacuo and the remaining volatile removed under high vacuum (15 minutes). The solid residue was dissolved in dry methylene chloride (20 ml) and a solution of 2-benzoyloxymethyl-4-acetoxy-1,3-oxathiolane (350 mg) in dry methylene chloride (20 ml) was added under argon,

followed by a solution f tin IV chloride ($SnCl_4$, 124 ml) in methylene chloride (20 ml) at 0°C. The reaction mixture was stirred under argon overnight at room temperature, then heated at refluxing for 3 hours and cooled to room temperature. The mixture was diluted with methylene chloride (100 ml) and poured while stirring into saturated aqueous $NaHCO_3$. The organic layer was separated by filtration over celite, washed first with water (2 x 75 ml), then with brine solution (100 ml), dried over $MgSO_4$ and filtered. The residue was purified by chromatography on silica gel using ethyl acetate:CH_3OH as the eluant to give 140 mg (35%) of the desired product as a mixture of cis- and trans- isomers in a 1:1 ratio as determined by ^1H-NMR. These isomers were separated as the N-acetyl derivatives in the next example.

Example 6

Cis- and trans-2-benzoyloxymethyl-4-(N_4,-acetyl-cytosin-1'-yl)-1,3-oxathiolane



(XXXII)

A solution of the cis- and trans- mixture of 2-benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane (135 mg), 4-dimethylaminopyridine (DMAP, 15 mg) and acetic anhydride (44 ml) in dry pyridine (10 ml) was stirred overnight at room temperature (16 hours) and poured into cold water (100 ml) followed, by extraction with methylene chloride (3 x 50 ml). The extract was washed with water, dried over $MgSO_4$, filtered and

evaporated in vacuo. Toluene was added to the residue, then evap rated in vacuo. T luene was added to the residue, then evaporated in vacuo and the residual oil was purified by chromatography on silica gel using ethyl acetate as eluant to yield 65 mg of pure trans-isomer as the fast moving product and 60 mg of pure cis-isomer as the low moving product. These were characterized by ^{1}H and ^{13}C-NMR.

cis-isomer:

^{1}H-NMR: δ(ppm in $CDCl_3$)

9.61 (b, 1H, C_4,-$NHCOCH_3$)
8.29 (d, 1H, C_6,-H)
8.06 (m, 2H, aromatic)
7.65 (m, 1H, aromatic)
7.51 (m, 2H, aromatic)
7.25 (d, 1H, C_5,-H)
6.61 (d, 1H, C_4-H)
5.50 (t, 1H, C_2-H)
4.80 (m, 2H, C_2-$CH_2OOCC_6H_5$)
4.48 (d, 1H, C_5-H)
4.05 (dd, 1H, C_5-H)
2.25 (s, 3H, CH_3)

^{13}C-NMR: δ(ppm in $CDCl_3$)

170.93, 166.28, 162.80, 155.76, 146.06, 133.91, 129.90, 128.84, 97.45, 85.88, 78.25, 64.60, 63.53 and 24.71.

trans-isomer:

^{1}H-NMR: δ(ppm in $DMSOd_6$)

10.88 (s, 1H, C_4,-$NHCOCH_3$)
8.13 (d, 1H, C_6,-H)
7.96 (m, 2H, aromatic)
7.68 (m, 1H, aromatic)
7.52 (m, 2H, aromatic)
7.20 (d, 1H, C_5,-H)
6.35 (d, 1H, C_4-H)
5.96 (dd, 1H, C_2-H)

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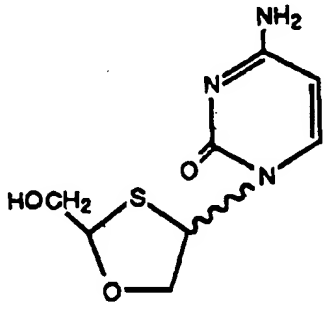
4.58 (dd, 1H, C_2-$CH_2OOCC_6H_5$)
4.44 (d, 1H, C_5-H)
4.29 (m, 2H, C_5-H and $CH_2OOCC_6H_5$)
2.07 (s, 3H, CH_3)

^{13}C-NMR: δ(ppm in $DMSOd_6$)
171.53, 165.84, 162.76, 155.21, 146.59, 134.00, 129.64, 129.23, 96.54, 83.78, 74.24, 64.58, 64.01 and 24.35

Example 7

Cis- and trans-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane



(XXXIII)

cis-isomer:

A solution of cis-2-benzoyloxymethyl-4(N_4,-acetyl-cytosin-1'-yl)-1,3-oxathiolane (54 mg) in methanolic ammonia (50 ml) was stirred overnight at room temperature (16 hours). The solvent was evaporated in vacuo and the residue treated with ether yielding 37 mg (90%) of desired product. The product was then characterized by ^{1}H- and ^{13}C-NMR.

m.p.: 213-215°C
UV:(CH_3OH) Lamda max: 270 nm
^{1}H-NMR: δ(ppm in, $DMSOd_6$)
7.85 (d, 1H, C_6,-H)
7.16 (d, 2H, C_4,-NH_2)
6.34 (d, 1H, C_4-H)
5.76 (d, 1H, C_5,-H)

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5.31 (t, 1H, C_2-CH_2OH)
5.18 (t, 1H, C_2-H)
4.40 (d, 1H, C_5-H)
3.92 (dd, 1H, C_5-H)
3.78 (m, 2H, C_2-CH_2OH)

^{13}C-NMR: δ(ppm in DMSOd_6)
165.95, 155.74, 142.39, 94.98, 88.85, 77.29, 62.91 and 62.48

trans-isomer:

A solution of trans-2-benzoyloxymethyl-4-(N_4,-acetyl-cytosin-1'-yl)-1,3-oxathiolane (63 mg) in methanolic ammonia (50 ml) was stirred overnight at room temperature (16 hours). The solvent was removed in vacuo and the residue was solidified with ether to give 36 mg (93%) of the desired product which was characterized by ^{1}H-and ^{13}C-NMR.

m.p.: 175-177°C

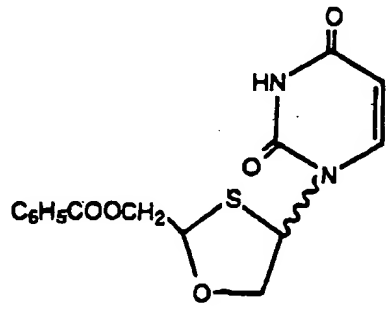
UV:(CH_3OH) Lamda max: 270 nm

^{1}H-NMR: δ(ppm in DMSOd_6)
7.67 (d, 1H, C_6,-H)
7.19 (d, 2H, C_4,-NH_2)
6.30 (d, 1H, C_4-H)
5.77 (d, 1H, C_5,-H)
5.56 (t, 1H, C_2-CH_2OH)
5.23 (t, 1H, C_2-H)
4.18 (m, 2H, C_5-H)
3.61 (m, 1H, C_2-CH_2OH)
3.36 (m, 1H, C_2-CH_2OH)

^{13}C-NMR: δ(ppm in DMSOd_6)
166.00, 155.65, 142.30, 95.11, 87.52, 74.52, 63.42 and 62.86

Example 8

Cis- and trans-2-benzoyloxymethyl-4(uracil-1'-yl)-1,3-oxathiolane



(XXXIV)

A mixture of uracil (446 mg), ammonium sulfate (20 mg) and hexamethyldisilazane (HMDS, 15 ml) was heated at refluxing under argon until the solution became clear (3 hours). Excess HMDS was removed under reduced pressure and the residue was dried under high vacuum for 3 hours. The oily residue was dissolved in dry methylene chloride (20 ml) and a solution of 2-benzoyloxymethyl-4-acetoxy-1,3-oxathiolane (748 mg) in dry methylene chloride (15 ml). The reaction mixture was stirred overnight at room temperature (20 hours) then poured into saturated aqueous $NaHCO_3$-solution (100 ml). The organic layer was collected and the aqueous phase was extracted with methylene chloride (2 x 50 ml). The combined organic phase was washed with water, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified and separated by chromatography on silica gel using hexane:ethyl acetate (1:4) as eluant. It gave 258 mg (29%) of a fast moving product, which was identified as trans-isomer and 156 mg (18%) of a low moving product, which was identified as cis-isomer.

cis-isomer:

^{1}H-NMR: δ(ppm in DMSOd_6)

11.39 (s, 1H, N_3,-H)

8.00 (d, 2H, aromatic)

7.97 (m, 2H, C_6,-H and aromatic)

7.56 (m, 2H, aromatic)
6.31 (d, 1H, C_4-H)
5.53 (t, 1H, C_2-H)
5.41 (d, 1H, C_5,-H)
4.76 (d, 2H, C_2-CH_2OH)
4.65 (d, 1H, C_5-H)
4.01 (dd, 1H, C_5-H)

^{13}C-NMR: δ(ppm in $DMSOd_6$).
165.83, 163.36, 151.06, 141.25, 134.15, 129.72, 129.50, 129.29, 102.83, 85.34, 76.60, 63.78 and 62.68

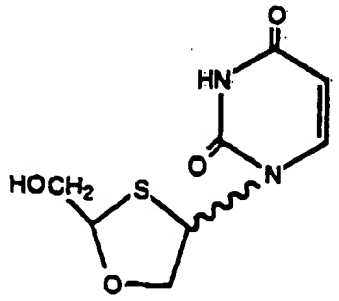
trans-isomer:

^{1}H-NMR: δ(ppm in $CDCl_3$)
9.10 (b, 1H, N_3,-H)
8.02 (d, 2H, aromatic)
7.53 (m, 2H, C_6,-H and aromatic)
7.43 (m, 2H, aromatic)
6.50 (d, 1H, C_4-H)
5.87 (dd, 1H, $C2_5$,-H)
5.76 (d, 1H, C_5,-H)
4.56 (dd, 1H, C_2-CH_2OBz)
4.30 (m, 2H, C_5,-H)
4.24 (dd, 1H, C_2-H_2OBz)

^{13}C-NMR: δ(ppm in $CDCl_3$)
166.28, 163.49, 150.89, 140.70, 133.59, 129.87, 129.42, 128.64, 103.72, 84.18, 75.18, 64.24 and 62.23

Example 9

Cis-and trans-2-hydroxymethyl-4-(uracil-1'-yl)-1,3-oxathiolane



(XXXV)

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cis-is mer:

A solution of cis-2-benzoyloxymethyl-4-(uracil-1'-yl)-1,3-oxathiolane (150 mg) in methanolic ammonia (50 ml) was stirred overnight at room temperature (16 hours). Solvent was evaporated in vacuo and the residue was triturated with ether (2 x 10 ml) and crystallized in ethyl acetate to yield 77 mg (75%) of desired product which was characterized by spectroscopic methods.

m.p.: 138-140°C

UV: (CH_3OH) Lamda max: 266 nm

^{1}H-NMR: δ(ppm in $DMSOd_6$)

11.36 (s, 1H, N_3,-H)
7.88 (d, 1H, C_6,-H)
6.28 (d, 1H, C_4-H)
5.66 (d, 1H, C_5,-H)
5.39 (t, 1H, C_2-CH_2OH)
5.19 (t, 1H, C_2-H)
4.55 (d, 1H, C_5-H)
3.95 (dd, 1H, C_5-H)
3.80 (m, 2H, C_2-CH_2OH)

^{13}C-NMR: δ(ppm in $DMSOd_6$).

163.54, 151.13, 141.87, 102.63, 89.13, 77.15, 62.45 and 62.04

trans-isomer:

A solution of trans-2-benzoyloxymethyl-4-(uracil-1'-yl)-1,3-oxathiolane (207 mg) in methanolic ammonia (50 ml) was stirred overnight at room temperature (16 hours) and then evaporated in vacuo. The residue was treated with ether (2 x 20 ml) and filtered. The solid residue was washed with cold ethyl acetate and yield 115 mg (81%) of pure product which was characterized by ^{1}H- and ^{13}C-NMR.

m.p.: 176-178°C

UV: (CH_3OH) Lamda max: 266 nm

^{1}H-NMR: δ(ppm in $DMSOd_6$)

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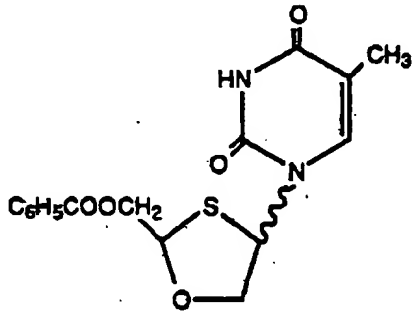
11.39 (s, 1H, N_3,-H)
7.66 (d, 1H, C_6,-H)
6.25 (d, 1H, C_4-H)
5.67 (d, 1H, C_5,-H)
5.62 (dd, 1H, C_2-H)
5.27 (t, 1H, C_2-CH_2OH)
4.35 (d, 1H, C_5-H)
4.16 (dd, 1H, C_5-H)
3.60 (m, 1H, C_2-CH_2OH)
3.35 (m, 1H, C_2-CH_2OH)

^{13}C-NMR: δ(ppm in DMSOd_6)
163.53, 151.15, 141.77, 102.78, 87.77, 74.28, 63.25 and 62.32

Example 10

cis- and trans-2-benzoyloxymethyl-4-(thymin-1'-yl)-1,3-oxathiolane



(XXXVI)

A mixture of thymine (671 mg), ammonium sulfate (20 mg) and hexamethyldisilazane (HMDS, 20 ml) was heated at refluxing until the solution became clear (3 hours). Excess reagent was evaporated in vacuo and the remaining volatile removed under high vacuum (1 hour). The oily residue was dissolved in dry methylene chloride (20 ml) and a solution of 2-benzoyloxymethyl-4-acetoxy-1,3-oxathiolane (1.05 g) in dry methylene chloride (20 ml) was added under argon, followed by a solution of trimethylsilyl trifluoromethane sulfonate (865 ml) in

methylene chlorid (5 ml). The reaction mixture was stirred overnight at r om temperature under argon (16 hours) and poured into saturated aqueous $NaHCO_3$-solution. The organic layer was separated and the aqueous phase extracted with methylene chloride (3 x 50 ml). The combined organic layer was washed with water (2 x 50 ml). The combined organic layer was washed first with water (2 x 50 ml), then with brine solution (100 ml), dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was purified and separated by chromatography on silica gel using hexane:ethyl acetate (1:1) as eluant to give 732 mg of a fast moving product which was identified by spectroscopic methods as trans-isomer and 244 mg of a lower moving product which was identified as cis-isomer. Total yield was 976 mg (75%).

cis-isomer:

^{1}H-NMR: δ(ppm in $DMSOd_6$)

11.41 (s, 1H, N_3,-H)
7.98 (d, 2H, aromatic)
7.72 (t, 1H, aromatic)
7.53 (t, 2H, aromatic)
7.47 (s, 1H, C_6,-H)
6.32 (d, 1H, C_2-H)
4.73 (m, 3H, C_5-H and C_2-$CH_2OOCC_6H_5$)
4.01 (dd, 1H, C_5-H)
1.58 (s, 3H, CH_3)

^{13}C-NMR: δ(ppm in $DMSOd_6$)

165.89, 164.00, 151.08, 136.37, 134.09, 129.63, 110.73, 85.30, 75.99, 63.68, 62.58 and 12.18

trans-isomer:

^{1}H-NMR: δ(ppm in $CDCl_3$)

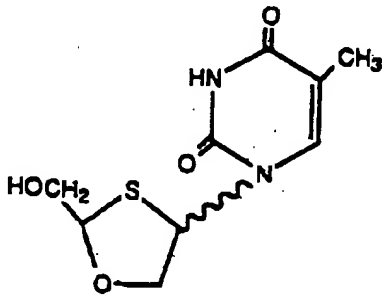
8.30 (s, 1H, N_3,-H)
8.04 (d, 2H, aromatic)
7.58 (t, 1H, aromatic)
7.45 (t, 2H, aromatic)
7.32 (d, 1H, C_6,-H, J = 1.3 Hz)

6.50 (dd, 1H, C_4-H)
5.90 (dd, 1H, C_2-H)
4.58 (dd, 1H C_2-$CH_2OCC_6H_5$)
4.30 (m, 2H, C_5-H)
4.24 (dd, 1H, C_2-$CH_2OOCC_6H_5$)
1.91 (d, 3H, $-CH_3$, J = 1.1 Hz)

^{13}C-NMR: δ(ppm in $CDCl_3$)
166.29, 163.91, 150.95, 136.14, 133.59, 129.88, 128.58, 112.48, 84.16, 75.04, 64.29, 62.35 and 12.41

Example 11

Cis- and trans-2-hydroxymethyl-4-(thymin-1'-yl)-1,3-oxathiolane



(XXXVII)

cis-isomer:

A solution of cis-2-benzoyloxymethyl-4-(thymin-1'-yl)-1,3-oxathiolane (190 mg) in saturated methanolic ammonia was stirred overnight at room temperature (16 hours). The mixture was evaporated under reduced pressure and the residue was purified by chromatography on silica gel using ethyl acetate as eluant to give 109 mg (82%) of pure product.

m.p.: 149-151°C

UV: (CH_3OH) Lamda max: 271.3 nm

^{1}H-NMR: δ(ppm in $DMSOd_6$)
11.37 (s, 1H, N_3,-H, D_2O-exchange)
7.79 (d, 1H, C_6,-H, J = 1.1 Hz)
6.30 (d, 1H, C_4-H, J = 4.4 Hz)

5.44 (t, 1H, C_2-CH_2OH, D_2O-exchange)
5.20 (t, 1H, C_2-H, J = 4.2 Hz)
4.52 (d, 1H, C_5-H, J = 10.7 Hz)
3.93 (dd, 1H, C_5-H, J = 4.90 and 10.7 Hz)
3.81 (m, 2H, C_2-CH_2OH)
1.78 (s, 3H, $-CH_3$)

^{13}C-NMR: δ(ppm in $DMSOd_6$)
164.15, 151.08, 137.44, 110.14, 89.09, 67.17, 62.18, 61.89 and 12.37

trans-isomer:

A mixture of trans-2-benzoyloxymethyl-4-(thymin-1'-yl)-1,3-oxathiolane (200 mg) in saturated methanolic ammonia (50 ml) was stirred overnight at room temperature (16 hours). The mixture was evaporated under reduced pressure and the residue was triturated with diethyl ether (3 x 15 ml) and filtered. The solid residue was recrystallized in ethanol to give 136 mg (97%) of pure product.

m.p.: 202-204°C

UV: (CH_3OH) Lamda max: 271.3 nm

^{1}H-NMR: δ(ppm in $DMSOd_6$)
11.40 (s, 1H, N_3,-H, D_2O exchange)
7.49 (s, 1H, C_6,-H)
6.26 (d, 1H, C_4-H)
5.67 (dd, 1H, C_2-H)
5.27 (t, 1H, C_2-CH_2OH, D_2O-exchange)
4.32 (d, 1H, C_5-H)
4.16 (dd, 1H, C_5-H)
3.58 (dd, 1H, C_2-CH_2OH)
3.33 (dd, 1H, C_2-CH_2OH)
1.80 (s, 3H, CH_3)

^{13}C-NMR: δ(ppm in $DMSOd_6$)
164.04, 150.90, 136.92, 110.44, 87.68, 74.06, 63.18, 61.98 and 12.19

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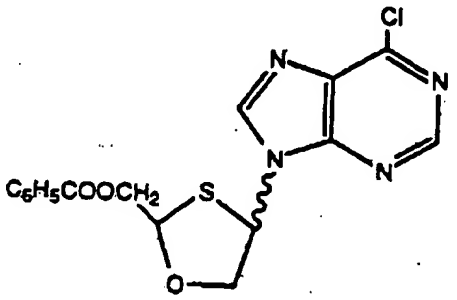
Example 12

Cis- and trans-2-benzoyloxymethyl-4-(6-chloropurin-9'-yl)-1,3-oxathiolane



(XI)

A mixture of 6-chloropurine (850 mg), ammonium sulfate (20 mg) and hexamethyldisilazane (HMDS, 20 ml) was heated at refluxing until the solution became clear. Excess reagent was evaporated in vacuo and the remaining volatile removed under high vacuum (1 hour). The oily residue was dissolved in dry dichloroethane (50 ml) and a solution of 2-benzoyloxymethyl-4-acetoxy-1,3-oxathiolane (1 g) in dry dichloroethane (20 ml) was added under argon, followed by a solution of trimethylsilyl trifluoromethane sulfonate (825 ml) in dry dichloroethane (5 ml). The mixture was heated at refluxing under argon for 2 hours, cooled to room temperature and poured into saturated aqueous $NaHCO_3$ solution. The organic layer was collected and the aqueous phase was extracted with methylene chloride (3 x 70 ml). The combined organic layer was washed first with water (2 x 50 ml), then with brine solution, dried over $MgSO_4$ and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by chromatography on silica gel using hexane:ethyl acetate (1:1) as eluant to give 435 mg of fast moving product which was identified as trans-isomer and 245 mg of lower moving product which was identified as cis-isomer. The total yield was 51%. Each isomer was characterized by ^1H- and ^{13}C-NMR spectroscopy.

cis-isomer:

^{1}H-NMR: δ(ppm in $CDCl_3$)

8.73 (s, 1H, C_8,-H)
8.53 (s, 1H, C_2,-H)
8.02 (d, 2H, aromatic)
7.56 (m, 1H, aromatic)
7.45 (m, 2H, aromatic)
6.51 (d, 1H, C_4-H, J = 3.8 Hz)
5.62 (t, 1H, C_2-H, J = 4.8 Hz)
4.78 (m, 2H, C_2-$CH_2OOCC_6H_5$)
4.69 (d, 1H, C_5-H, J = 10.4 Hz)
4.18 (dd, 1H, C_5-H, J= 4.0 and 10.6 Hz)

^{13}C-NMR: δ(ppm in $CDCl_3$)

165.83, 152.24, 151.80, 149.63, 145.48, 134.07, 129.58, 129.21, 85.42, 76.84, 64.48, and 61.75

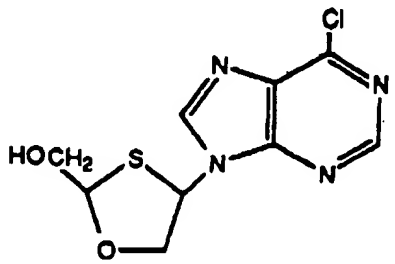
trans-isomer:

^{1}H-NMR: δ(ppm in $CDCl_3$)

8.74 (s, 1H, C_8,-H)
8.38 (s, 1H, C_2,-H)
8.05 (d, 2H, aromatic)
7.58 (m, 1H, aromatic)
7.45 (m, 2H, aromatic)
6.50 (d, 1H, C_4-H, J = 3.7 Hz)
6.03 (dd, 1H, C_2-H)
4.70 (dd, 1H, C_2-$CH_2OOCC_6H_5$)
4.50 (m, 2H, C_5-H)
4.32 (dd, 1H, C_2-$CH_2OOCC_6H_5$)

Example 13

Cis-2-hydroxymethyl-4-(6'-chloropurin-9-yl)-1,3-oxathiolane



(XII)

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A solution of cis-2-benzoyloxymethyl-4-(6'-chlor purin-9'-yl)-1,3-oxathiolane (300 mg) in methanolic ammonia (40 ml) was stirred overnight at room temperature (16 hours). The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel using EtOAc:MeOH (95:5) as eluant to give 189 mg (88%) of the desired product.

m.p.: 175-176°C

R_f: 0.68(EtOAc:MeOH)

UV: (H_2O) Lamda Max 263.5 nm

H-NMR: δ(ppm in $DMSOd_6$)

9.07 (s, 1H, C_8-H)

8.98 (s, 1H, C_2-H)

6.70 (d, 1H, C_4-H)

5.61 (t, 1H, C_2-CH_2OH, D_2O-exchange)

5.53 (t, 1H, C_2-H)

4.90 (d, 1H, C_5-H)

4.27 (dd, 1H, C_5-H)

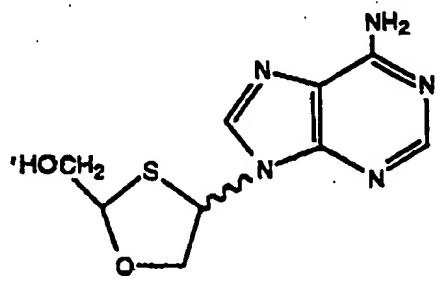
4.02 (m, 2H, C_2-CH_2OH)

^{13}C-NMR: δ(ppm in $DMSOd_6$)

152.17, 151.59, 149.58, 146.07, 131.17, 80.04, 77.37, 62.02, and 61.31

Example 14

Cis- and trans-2-hydroxymethyl-4-(adenin-9'-yl)-1,3-oxathiolane



(XIII)

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cis-isomer:

A mixture of cis-2-benzoyl xymethyl-4-(6-chloropurin-9'-yl)-1,3-oxathiolane (140 mg) in saturated ethanolic ammonia (50 ml) was placed in a steel bomb and heated overnight at 100-110°C (16 hours). The bomb was cooled to room temperature and emptied. The mixture was evaporated under reduced pressure and the residue was purified by chromatography on silica get using ethyl acetate:methanol (85:5) as eluant to give 70 mg (71%) of pure product.

m.p.: 200-202°C

UV: (CH_2OH) Lamda max: 260 nm

^{13}H-NMR: δ(ppm in $DMSOd_6$)

8.31 (s, 1H, C_8,-H)

8.16 (s, 1H, C_2,-H)

7.31 (s, 2H, C_6-NH_2, D_2O-exchange)

6.36 (d, 1H, C_4-H, J = 3.8 Hz)

5.41 (t, 1H, C_2-H, J = 3.8 Hz)

5.34 (t, 1H, C_2-CH_2OH, D_2O-exchange)

4.66 (d, 1H, C_5-H, J = 11.4 Hz)

4.09 (dd, 1H, C_5-H, J = 4.1 and 10.4 and 10.4 Hz)

3.83 (m, 2H, C_2-CH_2OH)

^{13}C-NMR: δ(ppm in $DMSOd_6$)

156.51, 153.09, 149.45, 139.19, 118.76, 89.06, 77.65, 62.79 and 60.13

trans-isomer:

A mixture of trans-2-benzoyloxymethyl-4-(6'-chloropurin-9'-yl)-1,3-oxathiolane (220 mg) in saturated ethanolic ammonia (50 ml) was placed in a steel bomb and heated overnight at 110°C for overnight (16 hours). The bomb was cooled to room temperature and emptied. The mixture was evaporated under reduced pressure and the residue was purified by chromatography on silica gel using EtOAc:MeOH (95:5) as eluant to give 76 mg (50%) the desired product.

m.p.: 185-187°C

UV: (CH_3OH) Lamda max: 260 nm

^{13}H-NMR: δ(ppm in $DMSOd_6$)

8.23 (s, 1H, C_8,-H)

8.17 (s, 1H, C_2,-H)

7.32 (s, 2H, C_6-NH_2, D_2O-exchange)

6.36 (d, 1H, C_4-H, J = 3.8 Hz)

5.75 (t, 1H, C_2-H, J = 5.7 Hz)

5.32 (t, 1H, C_2-CH_2OH, D_2O-exchange)

4.50 (d, 1H, C_5-H, J = 10.2 Hz)

4.35 (dd, 1H, C_5-H, J = 4.1 Hz and 10.0 Hz)

3.73 (m, 1H, C_2-CH_2OH)

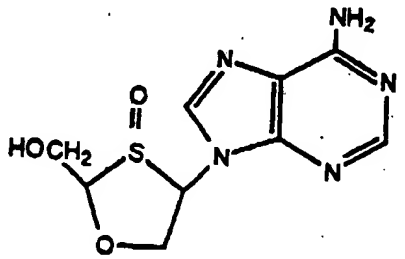
3.43 (m, 1H, C_2-CH_2OH)

^{13}C-NMR: δ(ppm in $DMSOd_6$)

165.53, 153.12, 149.40, 139.30, 119.00, 87.99, 74.70, 63.29 and 60.51

Example 15

Cis-2-hydroxymethyl-4-(adenin-9'-yl)-3-oxo-1,3-oxathiolane



(XIV)

A solution of 2-hydroxymethyl-4-(adenin-9'-yl)-1,3-oxathiolane (60 mg) in methanol (30 ml) was cooled at 0°C in an ice bath and meta-chloroperbenzoic acid (49 mg) was added slowly under stirring. The mixture was kept at this temperature for and solvent was evaporated under reduced pressure. The residue was triturated with diethyl either (2 x 15 ml) and purified on silica gel using EtOAc:MeOH (9:1) as eluant to give 49 mg of the product (77% yield). Surprisingly, only one diastereomer was formed. The product was characterized by H-and ^{13}C-NMR.

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UV: (H_2O) Lamda max: 258 nm

m.p.: Dec >192°C

^{1}H-NMR: δ(ppm in DMSOd_6)

8.24 (s, 1H, C_8,-H)

8.08 (s, 1H, C_2,-H)

7.41 (s, 2H, C_4,-NH_2, D_2O-exchange)

5.85 (d, 1H, C_4-H, J = 3.8 Hz)

5.52 (t, 1H, C_2-CH_2OH, D_2O-exchange)

5.17 (d, 1H, C_5-H, J = 11.6 Hz)

4.62 (dd, 1H, C_5-H, J = 4.1 and 11.8 Hz)

4.60 (t, 1H, C_2-H, J = 3.6 Hz)

4.02 (m, 1H, C_2-CH_2OH)

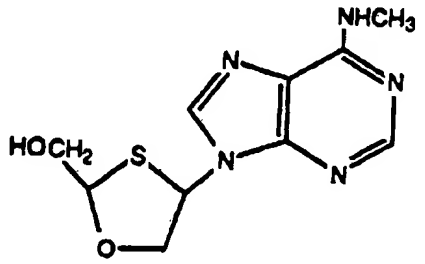
3.82 (m, 1H, C_2-CH_2OH)

^{13}C-NMR: δ(ppm in DMSOd_6)

156.66, 153.51, 149.83, 138.56, 118.61, 111.84, 75.99, 71.91 and 58.29

Example 16

Cis-2-hydroxymethyl-4-(6'-N-methylamino-purin-9'-yl)-1,3-oxathiolane



(XV)

A solution of cis-2-hydroxymethyl-4-(6'-chloropurin-9'-yl)-1,3-oxathiolane (144 mg) in ethanol (30 ml) was cooled at 0°C in an ice bath and methylamine gas was bubbled through the solution for 20 minutes. The mixture was placed in steel bomb and heated overnight at 110-115°C (16 hours). The bomb was cooled to room temperature and emptied. The mixture was evaporated in

vacuo and the residue was purified by chromatography on silica g l using EtOAc:MeOH (9:1) as eluant to give 102 mg (72%) of the desired product.

m.p.: 190-192°C

R_f: 0.43 (EtOAc:MeOH)

UV: (H_2O) Lamda max: 266 nm

^{1}H-NMR: δ(ppm in $DMSOd_6$)

8.31 (s, 1H, C_8,-H)

8.25 (s, 1H, C_2,-H)

7.79 (b, 1H, C_4,-NH)

6.38 (d, 1H, C_4-H, J = 3.8 Hz)

5.40 (t, 1H, C_2-CH_2-OH)

5.33 (t, 1H, C_2-H, J = 4.3 Hz)

4.64 (d, 1H, C_5-H, J = 10.5 Hz)

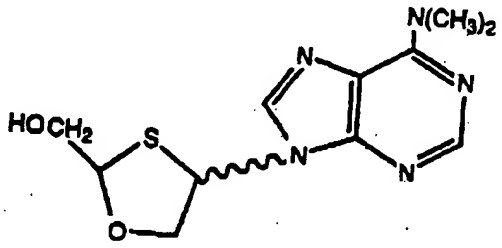
4.10 (dd, 1H, C_5-H, J = 4.3 and 10.5 Hz)

3.82 (m, 2H, C_2-CH_2-OH)

2.95 (s, 3H, C_4,-NCH_3)

Example 17

Cis- and trans-2-hydroxymethyl-4-(6'-dimethylamino purin-9'-yl)-1,3-oxathiolane



(XVI)

cis-isomer:

A solution of cis-2-benzoyloxymethyl-4-(6'-chloropurin-9'-yl)-1,3-oxathiolane (300 mg) in ethanol (60 ml) was cooled at 0°C in an ice bath and dimethylamine gas was bubbled through the solution for 20 minutes. The mixture was placed in a steel bomb and heated overnight at 110-115°C (16 hours). The bomb was cooled to room temperature and emptied. Solvent was removed in vacuo and the residue was purified by

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chromatography on silica gel using ethyl acetate as eluant to give 170 mg (76%) of the desired product.

m.p.: 124-126°C

R_f: 0.32 (EtOAc)

UV: (CH_3OH) Lamda max: 273 nm

^{1}H-NMR: δ(ppm in $DMSOd_6$)

8.32 (s, 1H, C_8,-H)

8.22 (s, 1H, C_2,-H)

6.37 (d, 1H, C_4,-H, J = 4.0 Hz)

5.38 (t, 1H, C_2-CH_2OH, D_2O-exchange)

5.32 (t, 1H, C_2-H, J = 4.3 Hz)

4.33 (d, 1H, C_5-H, J = 11.5 Hz)

4.08 (dd, 1H, C_5-H, J = 4.0 and 10.5 Hz)

3.80 (m, 2H , C_2-CH_2OH)

3.43 (b, 6H, C_6,-$N(CH_3)_2$)

trans-isomer:

A solution of trans-2-benzoyloxymethyl-4-(6'-chloropurin-9'-yl)-1,3-oxathiolane (500 mg) in ethanol (70 ml) was cooled at 0°C in an ice bath and dimethylamine gas was bubbled through the solution for 20 minutes. The mixture was placed in a steel bomb and heated overnight at 110°-115°C (16 hours). The bomb was cooled to room temperature and emptied. Solvent was removed in vacuo and the solid residue triturated with diethylether (2 x 30 ml) and recrystallized in ethanol to give 268 mg of the desired product (72% yield).

m.p.: 174-176°C

R_f: 0.30(EtOAc)

UV: (CH_3OH) Lamda max: 271 nm

^{1}H-NMR: δ(ppm in $DMSOd_6$)

8.23 (s, 1H, C_8,-H)

8.22 (S, 1H, C_2,-H)

6.36 (d, 1H, C_4-H, J = 3.0 Hz)

5.71 (dd, 1H, C_2H, J = 4.9 and 6.8 Hz)

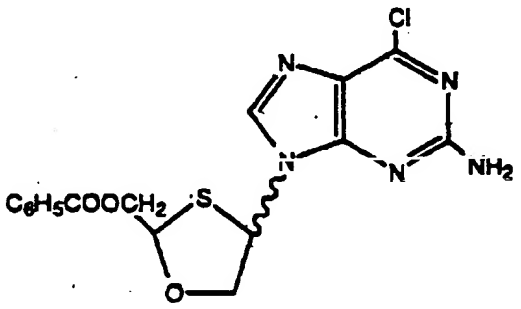
5.30 (t, 1H, C_2-CH_2OH, D_2O-exchange)

4.46 (dd, 1H, C_5-H, J = 3.3 and 12.4 Hz)

4.32 (dd, 1H, C_5-H, J = 4.3 and 10.4 Hz)
3.68 (m, 1H, C_2-CH_2OH)
3.43 (m, 7H, C_2-CH_2OH and C_6,-$N(CH_3)_2$)

Example 18

Cis- and trans-2-benzoyloxymethyl-4-(2'-amino-6'-chloro-purin-9-yl)-1,3-oxathiolane



(XXXVIII)

A mixture of 2-amino-6-chloropurine (6-chloroguanine, 1.3 g), ammonium sulfate (50 mg), and hexamethyldisilazane (HMDS, 30 ml) became clear (3 hours). Excess reagent was evaporated in vacuo and the remaining volatile removed under high vacuum (1 hour). The residue was dissolved in dry dichloroethane (75 ml) and a solution of 2-benzoyloxymethyl-4-acetoxy-1,3-oxathiolane (1.1 g), in dry dichloroethane (20 ml) was added under argon, followed by a solution of trimethylsilyl trifluoromethane sulfonate (1.5 ml) in dry dichloroethane (15 ml). The mixture was heated at refluxing under argon for 2 hours, cooled to room temperature and poured into saturated aqueous $NaHCO_3$ solution. After stirring for 15 minutes the organic layer was collected and the aqueous phase was extracted with methylene chloride (3 x 75 ml). The combined organic layer was washed with water (2 x 100 ml), then with brine solution, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo and the residue was purified by chromatography on silica gel using

hexane:ethyl acetate (1:1) as eluant to give 460 mg f a fast moving product which was identified as trans-isomer and 340 mg of low moving product which was identified as cis-isomer. The total yield was 52%.

cis-isomer:

m.p.: 192-194°C

R_f: 0.50 (hexane:ethyl acetate 3:7)

^{1}H-NMR: δ(ppm in $DMSOd_6$)

8.20 (s, 1H, C_8,-H)
7.89 (m, 2H, aromatic)
7.69 (m, 1H, aromatic)
7.52 (m, 2H, aromatic)
7.03 (s, 2H, C_2,-NH_2)
6.26 (d, 1H, C_4-H, J = 3.9 Hz)
5.66 (t, 1H, C_2-H, J = 6.00 Hz)
4.88 (d, 1H, C_5-H, J = 10.8 Hz)
4.73 (m, 2H, C_2-$CH_2OOCC_6H_5$)
4.16 (dd, 1H, C_5-H, J = 4.2 and 10.7 Hz)

trans-isomer:

m.p.: 186-188°C

R_f: 963 (hexane:ethyl acetate)

^{1}H-NMR: δ(ppm in $DMSOd_6$)

8.21 (s, 1H, C_8,-H)
8.01 (m, 2H, aromatic)
7.60 (m, 1H, aromatic)
7.57 (m, 2H, aromatic)
7.04 (s, 2H, C_2,-NH_2)
6.29 (d, 1H, C_4-H, J = 4.0 Hz)
6.11 (dd, 1H, C_2-H, J = 3.2 and 8.2 Hz)
4.63 (m, 2H, C_5-H and C_2-$CH_2OOCC_6H_5$)
4.38 (m, 2H, C_5-H and C_2-$CH_2OOCC_6H_5$)

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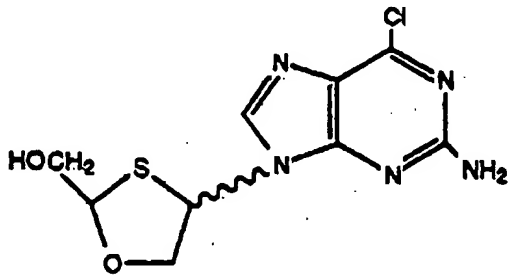
Example 19

Cis- and trans-2-hydroxymethyl-4-(2'-amino-6'-chloropurin-9'-yl)-1,3-oxathiolane



(XXXIX)

cis-isomer:

A solution of cis-2-benzoyloxymethyl-4-(2'-amino-6'-chloropurin-9'-yl)-1,3-oxathiolane (305 mg) in methanolic ammonia (100 ml) was stirred overnight at room temperature (16 hours). The mixture was evaporated under reduced pressure and the residue was triturated with diethyl ether (2 x 30 ml). The solid residue was recrystallized in ethanol to give pure 184 mg of product (82% yield).

m.p.: 194-196°C

R_f: 0.58 (EtOAc)

UV: (CH_3OH) Lamda max: 309 and 248 nm

^{1}H-NMR: δ(ppm in $DMSOd_6$)

8.30 (s, 1H, C_8,-H)

7.03 (s, 2H, C_2,-NH_2)

6.19 (d, 1H, C_4-H, J = 3.9 Hz)

5.41 (t, 1H, C_2-CH_2OH, D_2O-exchange)

5.33 (t, 1H, C_2-H, J = 4.1 Hz)

4.70 (d, 1H, C_5-H, J = 10.4 Hz)

4.06 (dd, 1H, C_5-H, J = 4.1 and 10.5 Hz)

3.82 (t, 2H, C_2-CH_2OH)

trans-isomer:

A solution of trans-2-benzoyloxymethyl-4-(2'-amino-6'-chloropurin-9'-yl)-1,3-oxathiolane (150 mg) in

methanolic ammonia (50 ml) was stirred overnight at room temperature (16 hours). Solvent was evaporated under reduced pressure and the residue purified by chromatography on silica gel using ethyl acetate as eluant to give 83 mg (76%) of pure product.

m.p.: 180-182°C

R_f: 0.50 (ethyl acetate)

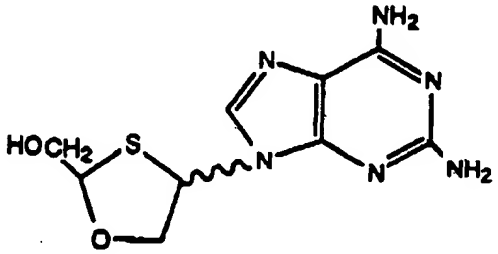
U.V. (CH_3OH) Lamda max: 309:5 and 248 nm

^1H-NMR: δ(ppm in $DMSOd_6$)

8.21 (s, 1H, C_8,-H)
7.03 (s, 2H, C_2,-NH_2)
6.20 (dd, 1H, C_4-H, J = 1.6 and 4.3 Hz)
5.74 (dd, 1H, C_2-H, J = 4.7 and 8.9 Hz)
5.31 (t, 1H C_2-CH_2OH, D_2O-exchange)
4.52 (dd, 1H, C_5-H, J = 1.7 and 10.4 Hz)
4.31 (dd, 1H, C_5-H, J = 4.4 and 10.4 Hz)
3.68 (g, 1H, C_2-CH_2OH)
3.44 (g, 1H, C_2-CH_2OH)

Example 20

Cis- and trans-2-hydroxymethyl-4-(2',6'-diaminopurin-9'-yl)-1,3-oxathiolane



(XL)

cis-isomer:

A mixture of cis-2-benzoyloxymethyl-4-(2'-amino-6'-chloropurin-9'-yl)-1,3-oxathiolane (175 mg) in saturated methanolic ammonia (50 ml) was placed in a steel bomb and heated overnight at 110-115°C (16 hours). The bomb was cooled to room temperature and emptied. The

mixture was evaporated to dryness and the solid residue triturated with diethyl ether (2 x 30 ml) and dissolved in methanol (100 ml). The solution was boiled with charcoal (2 g) for 5 minutes and filtered. The filtrate was evaporated in vacuo and the residue recrystallized in ethanol to give 90 mg of the product (75% yield).

m.p.: Dec.>250°C

R_f: 0.27 (EtOAc:MeOH 9:1)

UV: (CH_3OH) Lamda max: 281 and 258 nm

^{1}H-NMR: δ(ppm in $DMSOd_6$)

7.80 (s, 1H, C_8,-H)

6.94 (b, 2H, C_2,-NH_2, D_2O-exchange)

6.12 (d, 1H, C_4-H, J = 3.9 Hz)

6.00 (b, 2H, C_6,-NH_2, D_2O-exchange)

5.40 (b, 1H, C_2-CH_2OH, D_2O-exchange)

5.30 (t, 1H, C_2-H, J = 4.5 Hz)

4.61 (d, 1H, C_5-H, J = 10.4 Hz)

4.05 (dd, 1H, C_5-H, J = 4.2 and 10.4 Hz)

3.78 (m, 2H, C_2-CH_2OH)

trans-isomer:

A mixture of trans-2-benzoyloxymethyl-4-(2'-amino-6'-chloropurin-9'-yl)-1,3-oxathiolane (300 mg) in saturated methanolic ammonia (60 ml) was placed in a steel bomb and heated overnight at 110-115°C. The bomb was cooled to room temperature and emptied. The mixture was evaporated to dryness and the solid residue was triturated with diethyl ether (2 x 30 ml) and dissolved in methanol (100 ml). The solution was boiled with charcoal for 5 minutes and filtered. The filtrate was evaporated in vacuo and the residue was recrystallized in ethanol to give 149 mg (72%) of the desired product.

m.p.: 242-244°C

R_f: 0.23 (EtOAc:MeOH 9:1)

UV: (CH_3OH) Lamda max: 281 and 259 nm

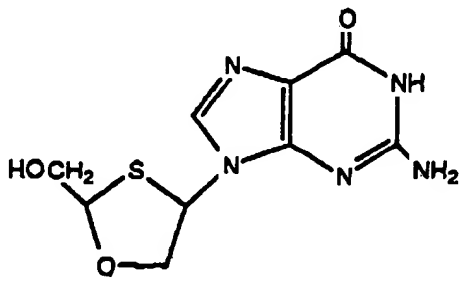
^{1}H-NMR: δ(ppm in $DMSOd_6$)

7.81 (s, 1H, C_8,-H)

6.78 (s, 2H, C_2,-NH_2, D_2O- xchange)
6.12 (d, 1H, C_4-H, J = 4.4 Hz)
5.90 (s, 2H, C_6,-NH_2,, D_2O-exchange)
5.70 (dd, 1H, C_2-H, J = 4.5 and 6.7 Hz)
5.31 (t, 1H, C_2-CH_2OH, D_2O-exchange)
4.44 (d, 1H, C_5,-H, J = 10.2 Hz)
4.29 (dd, 1H, C_5-H, J = 4.6 and 10.2 Hz)
3.67 (m, 1H, C_2-CH_2OH)
3.43 (m, 1H, C_2-CH_2OH)

Example 21

Cis-2-hydroxymethyl-4-(guanin-9'-yl)-1,3-oxathiolane



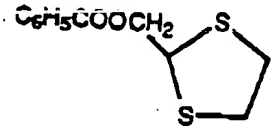
(XLI)

A mixture of cis-2-hydroxymethyl-4-(2'-amino-6'-chloropurin-9'-yl)-1,3-oxathiolane (100 mg), sodium hydroxide (3 g), water (5 ml) and methanol (20 ml) was heated overnight at refluxing (16 hours) and cooled to room temperature. The mixture was diluted with water (100 ml), neutralized with ion-exchange resin (in pyridinium form) and filtered. The residue was washed with water (100 ml), the combined aqueous solution evaporated in vacuo and the residue recrystallized in water ethanol to give 48 g (51%) the desired product.
m.p.: Dec>280°C
UV: (H_2O) Lamda max: 270 and 250 nm
^{1}H-NMR: δ(ppm in $DMSOd_6$)
10.67 (b, 1H, -NH)
7.86 (s, 1H, C_8,-H)
6.55 (b, 2H, C_2,-NH_2, D_2O- xchange)

6.06 (d, 1H, C_4-H, J = 3.9 Hz)
5.40 (b, 1H, C_2-CH_2OH, D_2O-exchange)
5.29 (t, 1H, C_2-H, J = 4.6 Hz)
4.61 (d, 1H, C_5-H, J = 10.4 Hz)
4.05 (dd, 1H, C_5-H, J = 4.4 and 10.8 Hz)
3.79 (m, 2H, C_2-CH_2OH)

Example 22

2-benzoyloxymethyl-1,3-dithiolane



(XIX)

A mixture of 2-benzoyloxyacetaldehyde (5.65 g), 1,2-ethanedithiol (3 ml) and paratoluenesulfonic acid (200 mg) in toluene (250 ml) was heated at refluxing under water removal conditions using a Dean Stark apparatus for 4 hours. The mixture was cooled to room temperature, washed first with saturated aqueous $NaHCO_3$ solution (1 x 60 ml), then with water (2 x 60 ml), and dried over reduced pressure. The residue was purified by chromatography on silica gel using hexane:ethyl acetate (9:1) as eluant to give 5.2 g of pure product which was characterized by ^1H- and ^{13}-C-NMR spectroscopy.

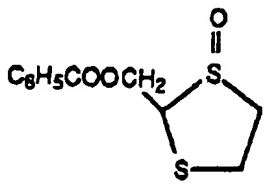
^1H-NMR: δ(ppm in $CDCl_3$)
8.07 (m, 2H, aromatic)
7.59 (m, 1H, aromatic)
7.44 (m, 2H, aromatic)
4.75 (t, 1H, C_2-H)
4.36 (d, 2H, C_2-$CH_2OOCC_6H_5$)
3.24 (s, 4H, C_4-H and C_5-H)

^{13}C-NMR: δ(ppm in $CDCl_3$)

166.27, 133.30, 129.85, 128.53, 68.15, 50.46 and 37.87

Example 23

2-benzoyloxymethyl-3-oxo-1,3-dithiolane



(XX)

2-Benzoyloxymethyl-1,3-dithiolane (5.2 g) was dissolved in dry methylene chloride (200 ml) and cooled to 0°C in an ice bath. Meta-chloroperbenzoic acid (80%, 4.67 g) in methylene chloride (100 ml) was added slowly while under stirring. The mixture was stirred at room temperature for 1 hour and then poured with into saturated aqueous $NaHCO_3$ solution (100 ml). The organic layer was separated, washed first with saturated $NaHCO_3$ solution (2 x 100 ml), then with water (100 ml), and finally with brine solution (100 ml), dried over $MgSO_4$ and filtered. The filtrate was evaporated in vacuo and the residue purified by chromatography on silica gel using ethyl acetate as eluant to give 4.0 g (74%) of pure product as a mixture cis- and trans-isomers.

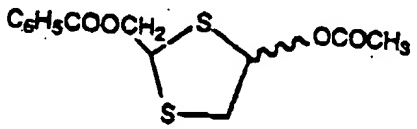
^{1}H-NMR: δ(ppm in $CDCl_3$)

8.09 (m, 2H, aromatic)
7.60 (m, 1H, aromatic)
7.46 (m, 2H, aromatic)
4.82 (dd, 1H, C_2-H, trans-isomers)
4.57 (m, 2H, C_2-$CH_2OOCC_6H_5$)
4.32 (dd, 1H, C_2-H, cis-isomer)
3.78 (m, 1H, C_4-H, trans-isomer)
3.59 (m, 2H, C_5-H, cis- and trans-isomer)
3.41 (m, 1H, C_4-H, cis-isomer)

2.87 (m, 1H, C_4-H, cis- and trans-isomer)

Example 24

Cis- and trans-2-benzoyloxymethyl-4-acetoxy-1,3-dithiolane



(XXI)

A mixture of 2-benzoyloxymethyl-3-oxo-1,3-dithiolane (5.1 g), sodium acetate (65 g) and acetic anhydride (100 ml) was heated at refluxing for 3 hours. Excess reagent was removed under reduced pressure. The residue was dissolved in methylene chloride (200 ml), washed first with saturated aqueous $NaCO_3$ solution (3 x 100 ml), then with water (100 ml), and finally with brine solution (100 ml), dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo and the residue purified by chromatography on silica gel using hexane:ethyl acetate (9:1) as eluant. The desired product was a byproduct and obtained in 9% yield (535 mg) as a mixture cis- and trans-isomer which was characterized by spectroscopic methods.

cis-isomer:

^{1}H-NMR: δ(ppm in $CDCl_3$)

8.01 (m, 2H, aromatic)
7.54 (m, 1H, aromatic)
7.41 (m, 2H, aromatic)
6.51 (t, 1H, C_4-H)
4.79 (t, 1H, C_2-H)
4.39 (dd, 1H, C_2-$CH_2OOCC_6H_5$)

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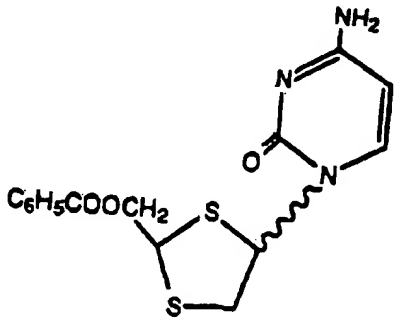
4.26 (dd, 1H, C_2-$CH_2OOCC_6H_5$)
3.34 (m, 2H, C_5-H)
2.05 (s, 3H, CH_3)

trans-isomer:

^{1}H-NMR: δ(ppm in $CDCl_3$)
8.04 (m, 2H, aromatic)
7.57 (m, 1H, aromatic)
7.42 (m, 2H, aromatic)
6.56 (t, 1H, C_4-H)
4.85 (t, 1H, C_2-H)
4.53 (m, 2H, C_2-$CH_2OOCC_6H_5$)
3.48 (d, 2H, C_5-H)
2.08 (s, 3H, CH_3)

Example 25

Cis- and trans-2-benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-dithiolane



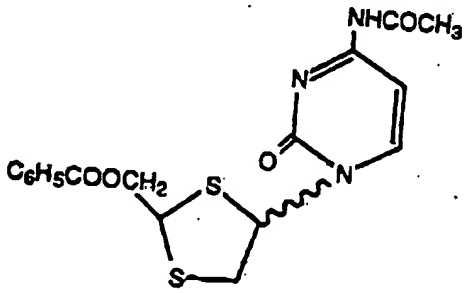
(XXII)

A mixture of cytosine (500 mg), ammonium sulfate (20 mg) and hexamethyldisilazane (15 ml) was heated at refluxing under argon until the solution became clear (3 hours). Excess reagent was evaporated under reduced pressure. The residue was dried under high vacuum for 1 hour and dissolved in dry methylene chloride (40 ml). A solution of 2-benzoyloxymethyl-4-acetoxy-1,3-dithiolane (882 mg) in dry methylene chloride (30 ml) was added under argon and the mixture was cooled at -10°C in an ice-salt bath. A solution of $SnCl_4$ (0.52 ml) in

methylene chloride (50 ml) was added and the mixture was stirred for 30 minutes and then heated overnight at refluxing (16 hours). The mixture was cooled to room temperature and poured into aqueous $NaHCO_3$ solution (100 ml). The organic layer was collected and the aqueous layer extracted with methylene chloride (2 x 100 ml) and filtered over celite. The combined organic layer was washed with water (2 x 100 ml), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate:methanol (9:1) as eluant to give 335 mg (32%) of the product in as a mixture of cis- and trans-isomers in a ratio of 1:1.2. The product was separated in next step as N-acetyl derivatives.

Example 26

Cis- and trans-2-benzoyloxymethyl-4-(N_4'-acetyl cytosin-1'-yl)-1,3-dithiolane



(XXIII)

A solution cis- and trans-2-benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-dithiolane (170 mg), 4-dimethylaminopyridine (20 mg), and acetic anhydride (0.1 ml) in dry pyridine (15 ml) was stirred overnight at room temperature (16 hours) and then poured into cold water (100 ml). The mixture was extracted with methylene chloride (3 x 75 ml), and the combined organic layer was washed with water (3 x 100 ml), dried over $MgSO_4$ and filtered. The filtrate was evaporat d in vacuo and the

residue was purified by chromatography on silica gel using thyl acetate as eluant to give pure trans-2-benzoyloxymethyl-4-(N_4,-acetyl cytosin-1'-yl)-1,3-dithiolane as the fast moving spot and pure cis-2-benzoyloxymethyl-4-(N_4,-acetyl cytosin-1'-yl)-1,3-dithiolane as the lower moving product. The two isomers were characterized by spectroscopic methods.

cis-isomer:

^{1}H-NMR: δ(ppm in $CDCl_3$)

9.51 (s, 1H, C_4,-NH-$COCH_3$)
8.49 (d, 1H, C_6,-H, J = 7.6 Hz)
8.04 (m, 2H, aromatic)
7.60 (m, 1H, aromatic)
7.45 (m, 2H, aromatic)
7.29 (d, 1H, C_5,-H, J = 7.6 Hz)
6.70 (d, 1H, C_4-H, J = 1.7 Hz)
4.99 (t, 1H, C_2-H, J = 2.6 Hz)
4.76 (m, 2H, C_2-$CH_2OOCC_6H_5$)
3.61 (dd, 1H, C_5-H, J = 4.2 and 13.5 Hz)
3.45 (d, 1H, C_5-H, J = 13.2 Hz)
2.25 (s, 3H, CH_3)

trans-isomer:

^{1}H-NMR: δ(ppm in $CDCl_3$)

9.50 (s, 1H, C_4,-NH-$COCH_3$)
8.24 (d, 1H, C_6,-H, J = 7.6 Hz)
8.03 (m, 2H, aromatic)
7.61 (m, 1H, aromatic)
7.46 (m, 3H, C_5,-H and aromatic)
6.76 (d, 1H, C_4-H, J = 3.6 Hz)
5.02 (t, 1H, C_2-H, J = 7.2 Hz)
4.49 (dd, 1H, C_2-$CH_2OOCC_6C_5$, J = 7.1 and 11.4 Hz)
4.37 (dd, 1H, C_2-$CH_2OOCC_6H_5$, J = 7.2 and 11.4 Hz)
3.62 (dd, 1H, C_5-H, J = 4.2 and 13 Hz)
3.43 (d, 1H, C_5-H, J = 14.5 Hz)
2.26 (s, 3H, CH_3)

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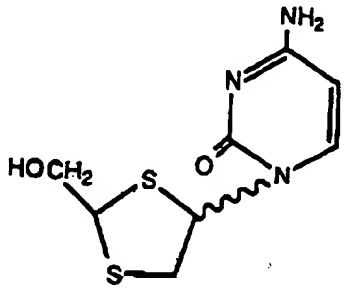
Example 27

Cis- and trans-2-hydroxymethyl-4-(cyt sin-1'-yl)-1,3-dithiolane



(XXIV)

cis-isomer:

A solution of cis-2-benzoyloxymethyl-4-(N_4,-acetyl cytosin-1'-yl)-1,3-dithiolane (10 mg) in methanolic ammonia (20 ml) was overnight stirred at room temperature (16 hours). The mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel using ethyl acetate:methanol (4:1) as eluant to give 3 mg (47%) of the desired product as a foam.

trans-isomer:

A solution of trans-2-benzoyloxymethyl-4-(N_4,-acetyl cytosin-1'-yl)-1,3-dithiolane (35 mg) in methanolic ammonia (20 ml) was stirred overnight at room temperature. The mixture was evaporated under reduced pressure and the residue was triturated with diethyl ether (2 x 10 ml) to give the desired product in 90% yield.

m.p.: 198-200°C

UV: (CH_3OH) Lamda max: 270 nm

^{1}H-NMR: δ(ppm in $DMSOd_6$):

7.91 (d, 1H, C_6,-H, J = 7.5 Hz)

7.19 (d, 2H, C_4,-NH_2, D_2O-exchange)

6.49 (d, 1H, C_4-H, J = 3.0 Hz)

5.71 (d, 1H, C_5,-H, J = 7.5 Hz)

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5.38 (t, 1H, C_2-CH_2OH, D_2O-exchange)
4.75 (t, 1H, C_2-H, J = 6.9 Hz)
3.40 (m, 4H, C_5-H and C_2-CH_2OH)
^{13}C-NMR: δ(ppm in $DMSOd_6$):
171.60, 160.93, 148.39, 98.86, 73.64, 71.56, 60.66 and 48.01

Example 28

Antiviral Activity: MT-4 Formazan Assay

Anti-HIV-1 antiviral activity was determined in MT-4 cells. A suspension of cells (approximately 10^6 cells/ml) in RPMI 1640 growth medium was infected with HIV-1 strain RF at a M.O.I. of 10^{-3} infectious units/cell. An uninfected cell suspension was prepared in parallel to evaluate drug-induced cytotoxicity. The two suspensions were incubated for 90 minutes at room temperature. Test compounds were serially diluted in 10-fold decrements from 100 µg/ml to 0.01 µg/ml (final concentrations in two 96 well microtitre plates. 20 µl of infected cell suspension were inoculated into each well of one of the plates (anti-viral), while 20 µl of uninfected cell suspension were added to each well of the second plate (cytotoxicity). The plates were then incubated for 7 days at 37°C. After incubation, 10 µl of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) at 20 mg/ml was added to all wells and the plates incubated for a further 90 minutes at 37°C.

150 µl of 10% (v/v) alcoholic Triton X-100 was then added and the cells resuspended. After 15 minutes at room temperature, the plates were analyzed in a Multiskan MC reader at 405 nm. Conversion of yellow MMT to its formazan derivative is maximum in uninfected cells, and absent in untreated infected cells. The optical density values for the cytotoxicity controls and the antiviral test wells were graphically plotted and the dose of compounds required to inhibit the conversion of

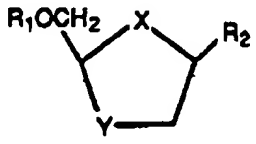
MMT to 50% of the untreated uninfected controls was calculated. In this way, both the 50% cytotoxic dose (CD 50%) and the 50% anti-viral dose (ID 50%) can be calculated. Table 1 shows CD 50% and ID 50% values obtained for cis-2-hydroxymethyl-4-(adenosine-9'-yl)-1,3-oxathiolane and 2',3'-dideoxyinosine.

Table 1

Compound	CD 50%	ID 50%
cis-XIII	100 µg/ml	2.1 µg/ml
ddI	100 µg/ml	2.3 µg/ml

CLAIMS:

1. A compound of formula (I), the geometric and optical isomers thereof, and mixtures of those isomers:



(I)

wherein:

X is selected from the group consisting of S, S=O, and SO_2;

Y is selected from the group consisting of O, S, S=O, and SO_2;

R_1 is hydrogen; and

R_2 is a purine or pyrimidine base or an analogue or derivative thereof; and

pharmaceutically acceptable derivatives thereof.

2. The compound according to claim 1 wherein Y is O.

3. The compound according to claim 1 wherein Y is S, S=O or SO_2.

4. The compound of formula (I) according to claim 1 wherein R_2 is selected the group consisting of:

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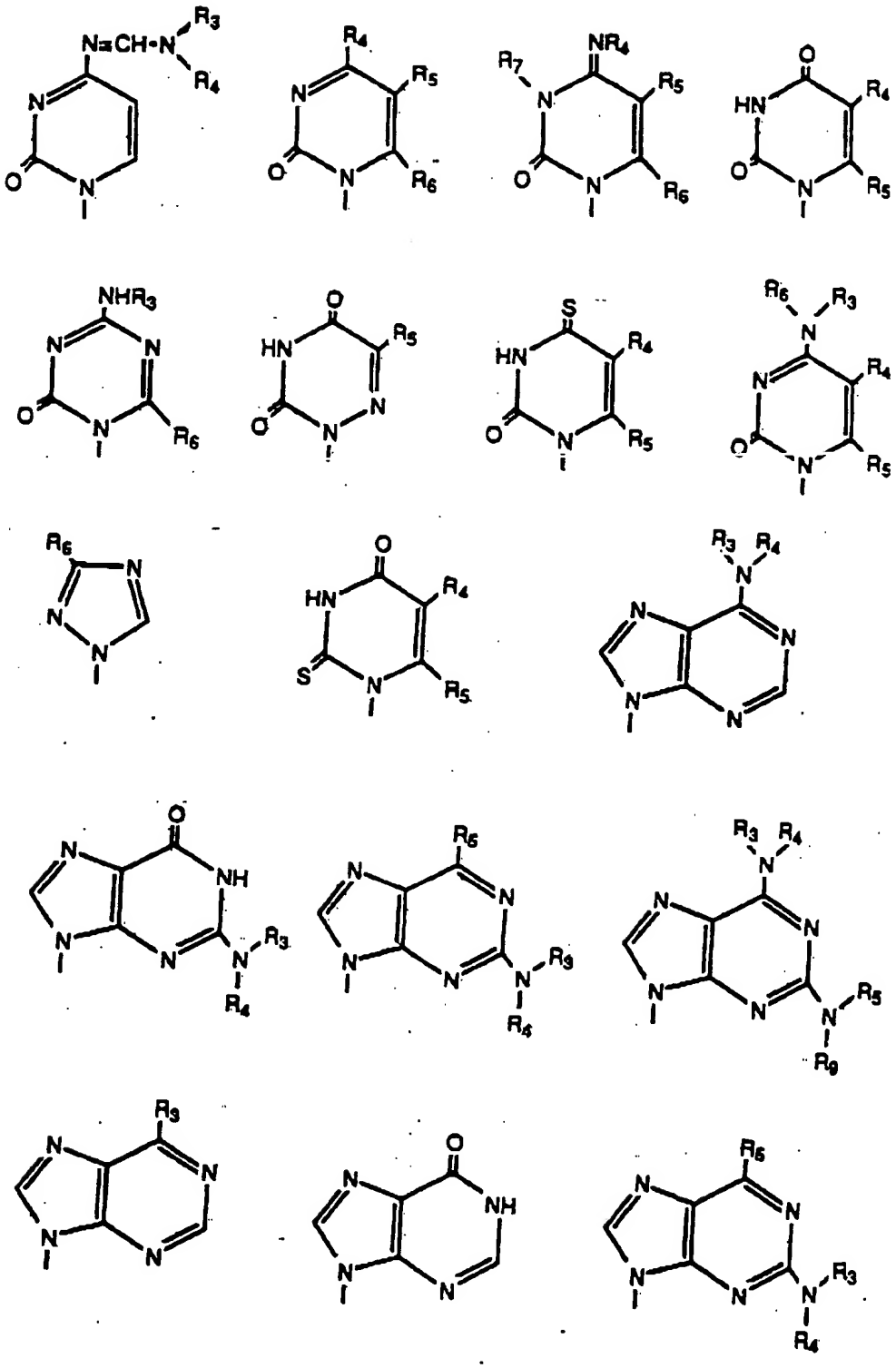

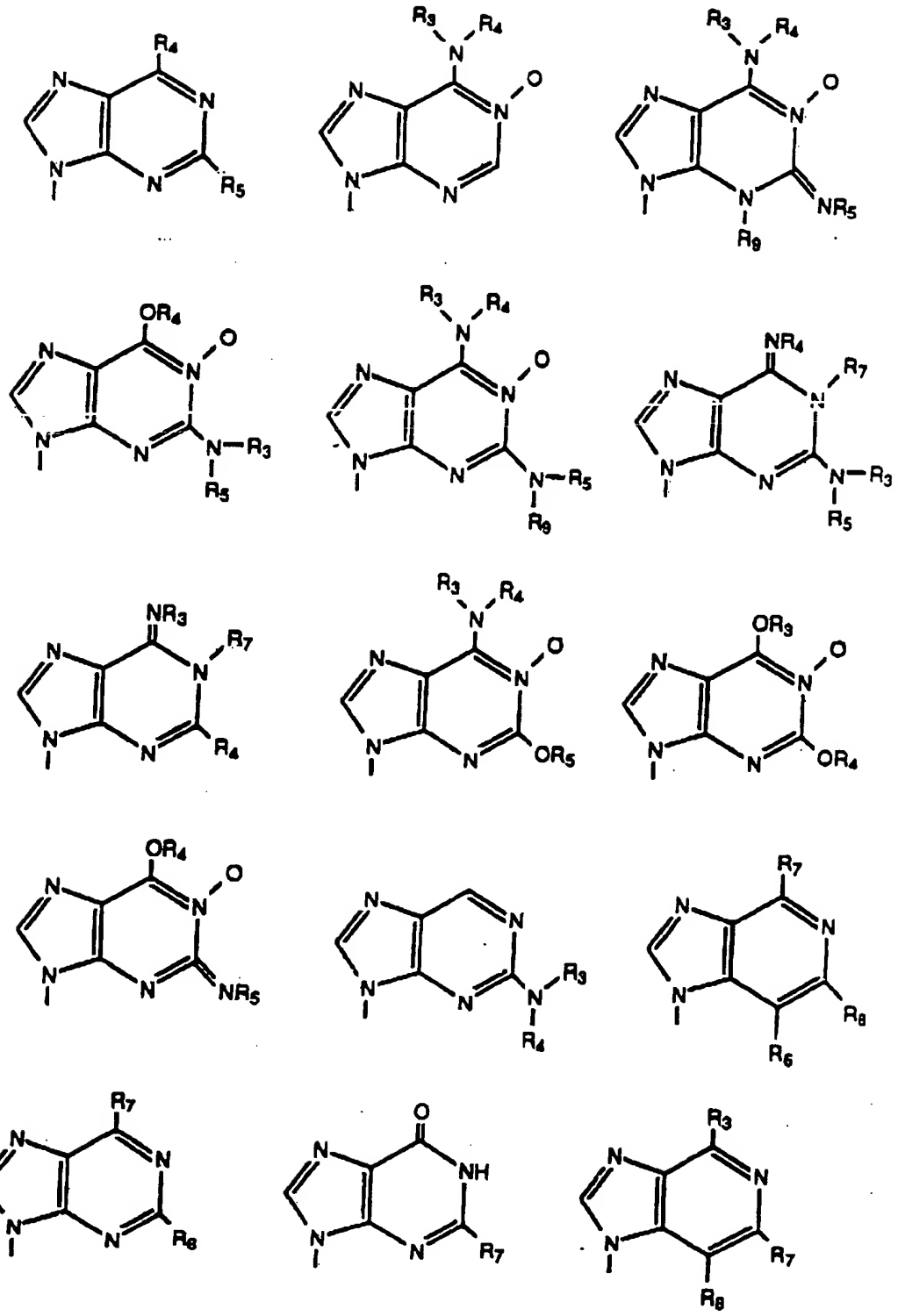

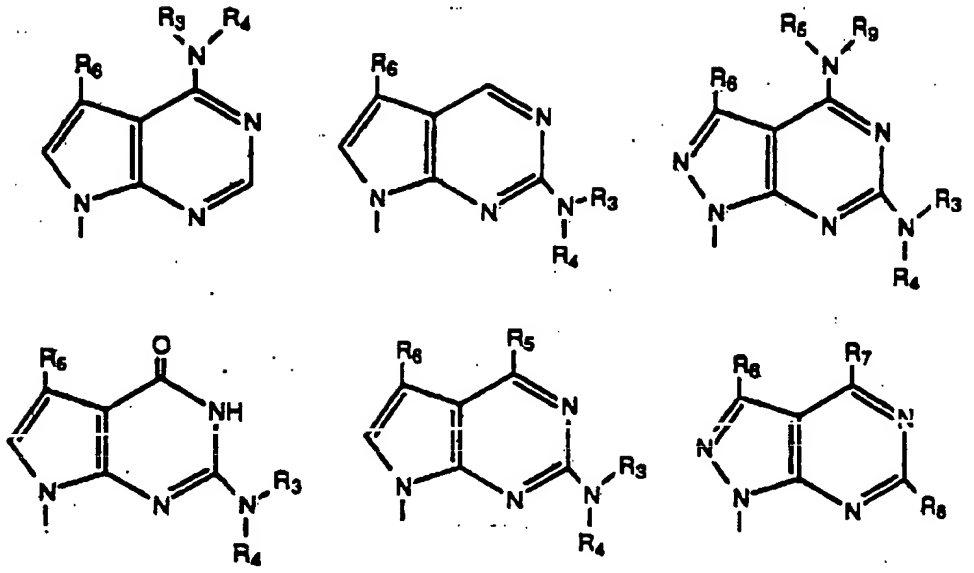

wherein:

R_3 is selected from the group consisting of hydrogen, C_{1-10} acyl, hydroxyl, substituted or unsubstituted C_{1-6} alkyl, and substituted or unsubstituted C_{1-6} alkenyl or alkynyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkenyl or alkynyl, bromine, chlorine, fluorine, iodine, and thioaryl;

R_6 is selected from the group consisting of hydrogen, bromine, chlorine, fluorine, iodine, cyano, carboxy, carboxamide, ethoxycarbonyl, carbamoyl, and thiocarbamoyl;

R_7 and R_8 are independently selected from the group consisting of hydrogen, bromine, chlorine, fluorine, iodine, substituted or unsubstituted amino, and hydroxy; and

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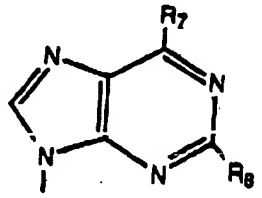
R_9 is selected from the group consisting of hydrogen, C_{1-10} acyl, hydroxyl, substituted or unsubstituted C_{1-6} alkyl, and substituted or unsubstituted C_{1-6} alkenyl or alkynyl.

5. The compound according to claim 4 wherein R_2 is

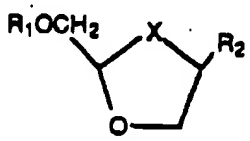


wherein:

R_7 and R_8 are independently selected from the group consisting of hydrogen, bromine, chlorine, fluorine, iodine, substituted or unsubstituted amino, and hydroxy.

6. The compound according to any one of claims 1 to 5 in the form of its cis isomer.

7. A compound of formula (Ia), the geometric and optical isomers thereof, and mixtures of those isomers:



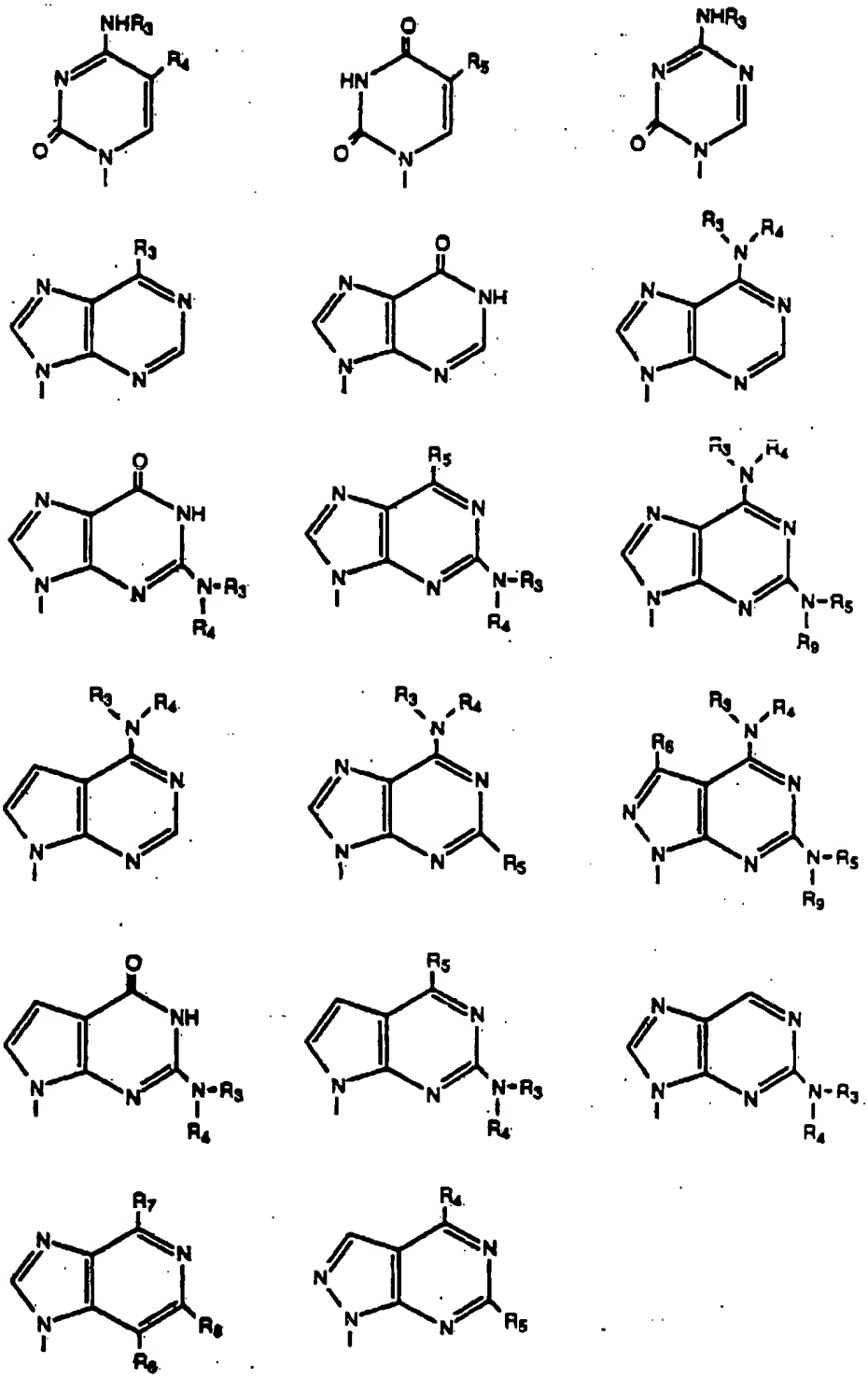
(Ia)

wherein:

X is selected from the group consisting of S, S=O, and SO_2;

R_1 is hydrogen; and

R_2 is selected from the group consisting of



wher in:

R_3 is selected from the group consisting of hydrogen, C_{1-10} acyl, hydroxyl, substituted or unsubstituted C_{1-6} alkyl, and substituted or unsubstituted C_{1-6} alkenyl or alkynyl;

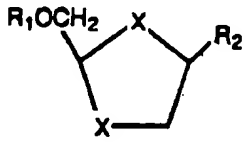
R_4 and R_5 are independently selected from the group consisting of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkenyl or alkynyl, bromine, chlorine, fluorine, iodine, and thioaryl;

R_6 is selected from the group consisting of hydrogen, bromine, chlorine, fluorine, iodine, cyano, carboxy, carboxamide, ethoxycarbonyl, carbamoyl, and thiocarbamoyl;

R_7 and R_8 are independently selected from the group consisting of hydrogen, bromine, chlorine, fluorine, iodine, substituted or unsubstituted amino, and hydroxy; and

R_9 is selected from the group consisting of hydrogen, C_{1-10} acyl, hydroxyl, substituted or unsubstituted C_{1-6} alkyl, and substituted or unsubstituted C_{1-6} alkenyl or alkynyl; and and pharmaceutically acceptable derivatives thereof.

8. A compound of formula (Ib), the geometric and optical isomers thereof, and mixtures of those isomers:



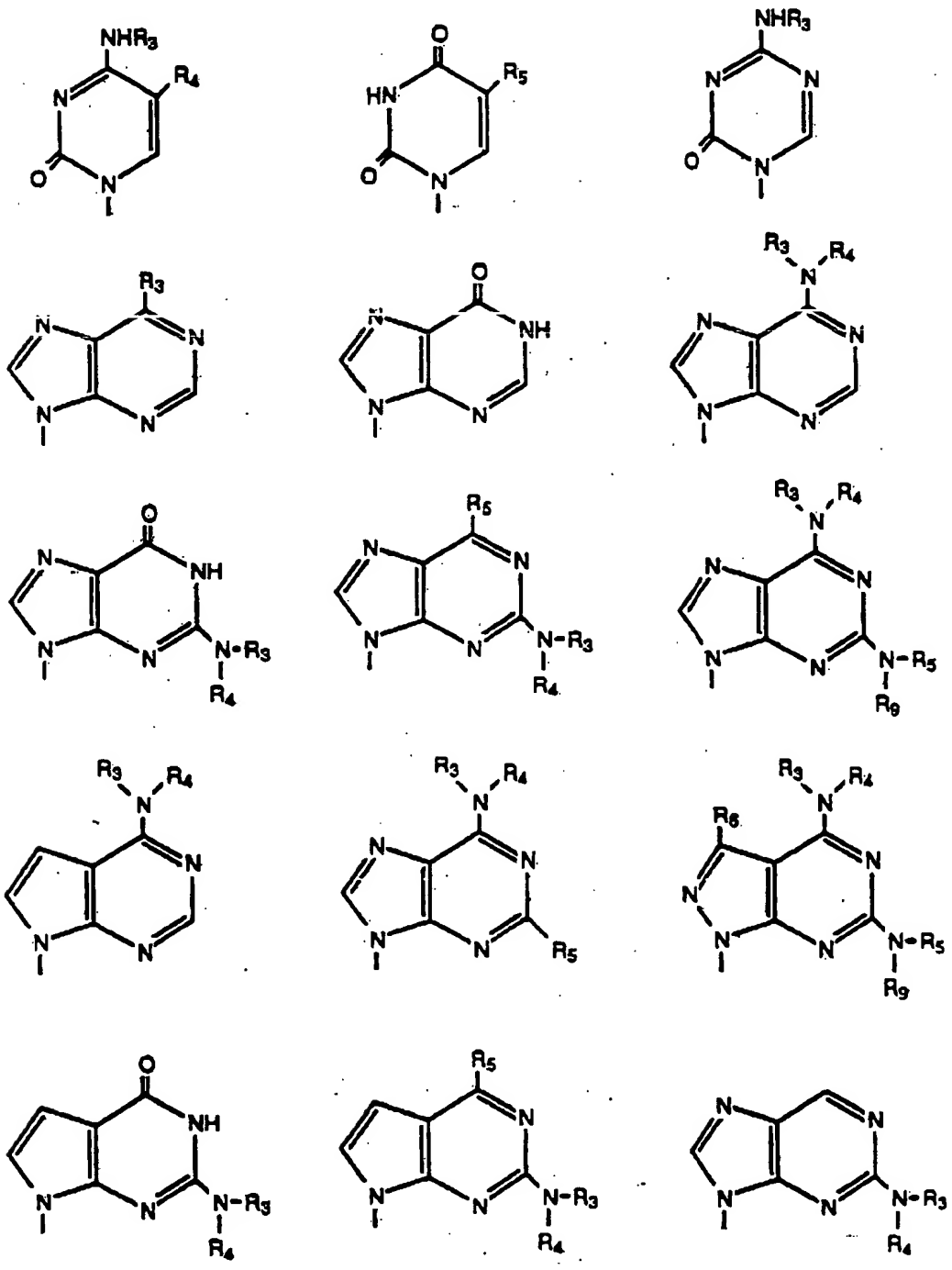
(Ib)

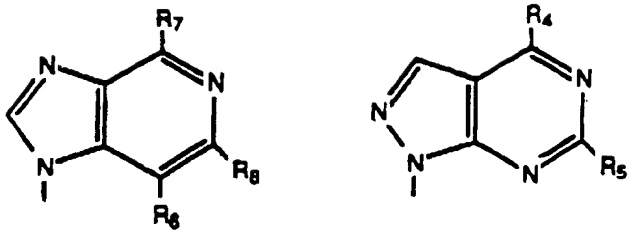
wherein:

each X is independently selected from the group consisting of S, S=O, and SO_2;

R_1 is hydrogen; and

R_2 is selected from the group consisting of





wherein:

R_3 is selected from the group consisting of hydrogen, C_{1-10} acyl, hydroxyl, substituted or unsubstituted C_{1-6} alkyl, and substituted or unsubstituted C_{1-6} alkenyl or alkynyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkenyl or alkynyl, bromine, chlorine, fluorine, iodine, and thioaryl;

R_6 is selected from the group consisting of hydrogen, bromine, chlorine, fluorine, iodine, cyano, carboxy, carboxamide, ethoxycarbonyl, carbamoyl, and thiocarbamoyl;

R_7 and R_8 are independently selected from the group consisting of hydrogen, bromine, chlorine, fluorine, iodine, substituted or unsubstituted amino, and hydroxy; and

R_9 is selected from the group consisting of hydrogen, C_{1-10} acyl, hydroxyl, substituted or unsubstituted C_{1-6} alkyl, and substituted or unsubstituted C_{1-6} alkenyl or alkynyl; and and pharmaceutically acceptable derivatives thereof.

9. The compound according to claim 1 selected from the group consisting of:

cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-4-(cytosin-1'-yl)-

1,3- xathiolan , and mixtures thereof;

cis-2-hydroxymethyl-4-(N_4'-acetyl-cyt sin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-4-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-hydroxymethyl-4-(uracil-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-4-(uracil-1'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-hydroxymethyl-4-(thymin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-4-(thymin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-hydroxymethyl-4-(6'-chloropurin-9'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-4-(6'-chloropurin-9'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-hydroxymethyl-4-(adenin-9'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-4-(adenin-9'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-hydroxymethyl-3-oxo-4-(adenin-9'-yl)-1,3-oxathiolane;

cis-2-hydroxymethyl-4-(6'-N-methylamino-purin-9'-yl)-1,3-oxathiolane;

cis-2-hydroxymethyl-4-(6'-N,N-dimethylamino-purin-9'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-4-(6'-N,N-dimethylamino-purin-9'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-hydroxymethyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-4-(2'-chloro-amino-6'-purin-9'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-hydroxymethyl-4-(2',6'-diamino-purin-9'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-4-(2',6'-diamino-purin-9'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-hydroxymethyl-4-(guanin-9'-yl)-1,3-oxathiolane;

cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-dithiolane, trans-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-dithiolan , and mixtures thereof;

cis-2-hydroxymethyl-4-(N_4'-acetyl-cytosin-1'-yl)-1,3-dithiolane, trans-2-hydroxymethyl-4-(N_4'-acetyl-cytosin-1'-yl)-1,3-dithiolane, and mixtures thereof; and pharmaceutically acceptable derivatives thereof in the form of a racemic mixture or single enantiomer.

10. The compound according to claim 9 selected from the group consisting of:

cis-2-hydroxymethyl-4-(adenin-9'-yl)-1,3-oxathiolane; and

pharmaceutically acceptable derivatives thereof in the form of a racemic mixture or single enantiomer.

11. The compound according to any one of claims 1, 7 or 8 in the form of a racemic mixture.

12. The compound according to any one of claims 1, 7 or 8 substantially in the form of a single enantiomer.

13. A pharmaceutical formulation effective against viral infections comprising a pharmaceutically effective amount of a compound according to any one of claims 1, 7 or 8 and a pharmaceutically acceptable carrier.

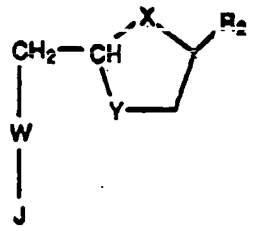
14. The pharmaceutical formulation according to claim 13 additionally comprising a further therapeutic agent.

15. A method of treating viral infections in mammals comprising the step of administering to said mammal the pharmaceutical formulation according to claim 13 or 14.

16. The method according to claim 15, wherein said viral infection is caused by human immunodeficiency virus and said mammal is a human.

17. The method according to claim 15, wherein said viral infection is caused by hepatitis B virus and said mammal is a human.

18. An ester of formula (IV) the geometric and optical isomers thereof, and mixtures of those isomers:



(IV)

wherein:

W is selected from the group consisting of PO_4^-, SPO_3^-, and $-O-C-(CH_2)_n-C-O-$ where n is an integer of 1 to 10;

J is any nucleoside or nucleoside analog or derivative thereof;

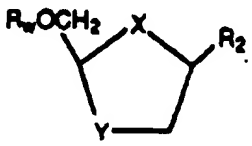
X is selected from the group consisting of S, S=O and SO_2,

Y is selected from the group consisting of O, S, S=O, and SO_2; and

R_2 is a purine or pyrimidine base or analogue or derivative thereof.

19. The ester according to claim 18 wherein J is:

20. An intermediate of formula (Ic), th geometric and optical isomers thereof, and mixtures of those isomers, useful for the production of substituted 1,3-oxathiolanes and substituted 1,3-dithiolanes with antiviral properties:



(Ic)

wherein:

X is selected from the group consisting of S, S=O, and SO_2;

Y is selected from the group consisting of O, S, S=O, and SO_2;

R_v is selected from the group consisting of trisubstituted silyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted aralkyl, and substituted or unsubstituted C_{1-16} acyl; and

R_2 is a purine or pyrimidine base or an analogue or derivative thereof.

21. The intermediate according to claim 20 wherein R_v is selected from the group consisting of benzyl, trityl, benzoyl and a benzoyl which may be substituted in any position by at least one group selected from the group consisting of bromine, chlorine, fluorine, iodine, C_{1-6} alkyl, C_{1-6} alkoxy, nitro and trifluoromethyl.

22. The intermediate according to claim 20 useful for the production of substituted 1,3-oxathiolanes with antiviral properties selected from the group consisting of:

cis-2-benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-b nzoyloxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-benzoyloxymethyl-4-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-4-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-benzoyloxymethyl-4-(uracil-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-4-(uracil-1'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-benzoyloxymethyl-4-(thymin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-4-(thymin-1'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-benzoyloxymethyl-4-(6'-chloropurin-9'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-4-(6'-chloropurin-9'-yl)-1,3-oxathiolane, and mixtures thereof;

cis-2-benzoyloxymethyl-4-(adenin-9'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-4-(adenin-9'-yl)-1,3-oxathiolane;

cis-2-benzoyloxymethyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-4-(2'-amino-6'-chloro-purin-9'-yl)-1,3-oxathiolane, and mixtures thereof.

23. The intermediate according to claim 20 useful for the production of substituted 1,3-dithiolanes with antiviral properties selected from the group consisting of:

cis-2-benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-dithiolane, trans-2-benzoyloxymethyl-4-(cytosin-1'-yl)-1,3-dithiolane, and mixtures thereof;

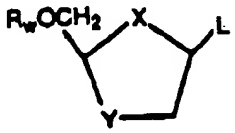
cis-2-benzoyloxymethyl-4-(N_4'-acetyl-cytosin-1'-yl)-1,3-dithiolane, trans-2-benzoyloxymethyl-4-(N_4'-acetyl-cytosin-1'-yl)-1,3-dithiolane, and mixtures thereof;

cis-2-t-butyldiphenylsilyloxymethyl-4-(cytosin-1'-yl)-1,3-dithiolane, trans-2-t-butyldiphenylsilyloxy-

methyl-4-(cytosin-1'-yl)-1,3-dithiolane, and mixtures thereof; and

cis-2-t-butyldiphenylsilyloxymethyl-4-(N_4'-acetoxy-cytosin-1'-yl)-1,3-dithiolane, trans-2-t-butyldiphenyl-silyloxymethyl-4-(N_4'-acetoxy-cytosin-1'-yl)-1,3-dithiolane, and mixtures thereof.

24. An intermediate of formula (Id), the geometric and optical isomers thereof, and mixtures of those isomers, useful for the production of substituted 1,3-oxathiolanes and substituted 1,3-dithiolanes with antiviral properties:



(Id)

wherein:

X is selected from the group consisting of S, S=O, and SO_2;

Y is selected from the group consisting of O, S, S=O, and SO_2;

R_w is selected from the group consisting of trisubstituted silyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted aralkyl, and substituted or unsubstituted C_{1-16} acyl; and

L is a leaving group.

25. The intermediate according to claim 24 wherein R_w is selected from the group consisting of benzyl, trityl, benzoyl and a benzoyl which may be substituted in any position by at least one group selected from the group consisting of bromine,

chlorine, fluorine, iodine, C_{1-6} alkyl, C_{1-6} alkoxy, nitro and trifluoromethyl.

26. The intermediate according to claim 24 useful for the production of substituted 1,3-oxathiolanes with antiviral properties selected from the group consisting of:

2-benzoyloxymethyl-1,3-oxathiolane;

cis-2-benzoyloxymethyl-1-oxo-1,3-oxathiolane, trans-2-benzoyloxymethyl-1-oxo-1,3-oxathiolane, and mixtures thereof;

cis-2-benzoyloxymethyl-4-acetoxy-1,3-oxathiolane, trans-2-benzoyloxymethyl-4-acetoxy-1,3-oxathiolane, and mixtures thereof;

27. The intermediate according to claim 24 useful for the production of substituted 1,3-dithiolanes with antiviral properties selected from the group consisting of:

2-t-butyldiphenylsilyloxymethyl-1,3-dithiolane;

2-benzoyloxymethyl-1,3-dithiolane;

cis-2-benzoyloxymethyl-3-oxo-1,3-dithiolane, trans-2-benzoyloxymethyl-3-oxo-1,3-dithiolane, and mixtures thereof;

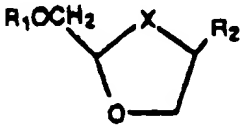
cis-2-benzoyloxymethyl-4-acetoxy-1,3-dithiolane, trans-2-benzoyloxymethyl-4-acetoxy-1,3-dithiolane, and mixtures thereof;

cis-2-t-butyldiphenylsilyloxymethyl-4-hydroxy-1,3-dithiolane, trans-2-t-butyldiphenylsilyloxymethyl-4-hydroxy-1,3-dithiolane, and mixtures thereof; and

cis-2-t-butyldiphenylsilyloxymethyl-4-acetoxy-1,3-dithiolane, trans-2-t-butyldiphenylsilyloxymethyl-4-acetoxy-1,3-dithiolane, and mixtures thereof.

28. A process for preparing a 1,3-oxathiolane compound of f rmula (Ia), the geometric and optical isomers thereof, and mixtures of those isomers:

(Ia)



wherein:

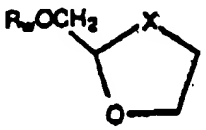
X is selected from the group consisting of S, S=O, and SO_2;

R_1 is hydrogen; and

R_2 is a purine or pyrimidine base or an analogue or derivative thereof;

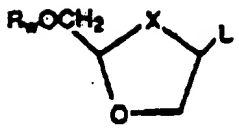
the process comprising the steps of:

a) condensing an aldehyde having of the formula R_vOCH_2CHO, wherein R_v is selected from the group consisting oftrisubstituted silyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted aralkyl, and substituted or unsubstituted C_{1-16} acyl, with a mercaptoalcohol in an organic solvent containing an acid catalyst to produce an intermediate of the formula:



b) treating the intermediate of step (a) with a peracid to give a corresponding sulfoxide;

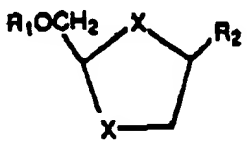
c) treating the intermediate of step (b) with an anhydride of the formula $(R_z)_2O$, wherein R_z is substituted or unsubstituted C_{1-6} alkyl, in the presence of a buffer to pr duce an intermediate of the formula:



wherein L is a leaving group;

d) treating the intermediate of step (c) with a silylated pyrimidine or purine base or analogue thereof, in the presence of a Lewis acid and hydrolyzing the R_v function to produce a compound of the formula (Ia).

29. A process for preparing a 1,3-dithiolane compound of formula (Ib), the geometric and optical isomers thereof, and mixtures of those isomers:



(Ib)

wherein:

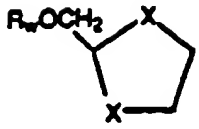
each X is independently selected from the group consisting of S, S=O, and SO_2;

R_1 is hydrogen; and

R_2 is a purine or pyrimidine base or an analogue or derivative thereof;

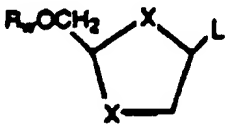
the process comprising the steps of:

a) condensing an aldehyde having of the formula R_vOCH_2CHO, wherein R_v is selected from the group consisting oftrisubstituted silyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted aralkyl, and substituted or unsubstituted C_{1-16} acyl, with a vicinal dithiol in an organic solvent containing an acid catalyst to produce an intermediate of the formula:



b) treating the intermediate of step (a) with a paracid to give a corresponding sulfoxide;

c) treating the intermediate of step (b) with an anhydride of the formula $(R_x)_2O$, wherein R_x is substituted or unsubstituted C_{1-6} alkyl, in the presence of a buffer to produce an intermediate of the formula:

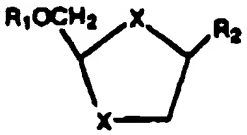


wherein L is a leaving group;

d) treating the intermediate of step (c) with a silylated pyrimidine or purine base or analogue thereof containing an NH_2 group, in the presence of a Lewis acid;

e) acetylation of the NH_2 group and hydrolyzing the R_w function to produce a compound of the formula (Ib).

30. A process for preparing a 1,3-dithiolane compound of formula (Ib), the geometric and optical isomers thereof, and mixtures of those isomers:



(Ib)

wherein:

X is selected from the group consisting of S, S=O, and SO_2;

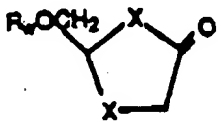
Y is selected from the group consisting of S, S=O, and SO_2;

R_1 is hydrogen; and

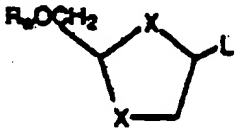
R_2 is a purine or pyrimidine base or an analogue or derivative thereof;

the process comprising the steps of:

a) reacting mercaptothioacetic acid with an aldehyde of formula R_vOCH_2CHO in an organic solvent in the presence of a Lewis acid to produce an intermediate of the formula:



b) reducing the intermediate of step (a) in an organic solvent and reacting the reduced intermediate with an acid anhydride or acid chloride in the presence of pyridine and an acetylation catalyst to give an intermediate of the formula:



wherein L is a leaving group;

c) treating the intermediate of step (b) with a silylated pyrimidine or purine in the presence of a Lewis acid and cleavage of the R_v function to produce a compound of the formula (Ib).

31. The process for preparing a 1,3-dithiolane according to claim 30, wherein R_v is a silyl protecting group.

INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 91/00407

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)*

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 409/04 C 07 D 411/04 C 07 D 473/02
A 61 K 31/505 C 07 F 7/18

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 409/00 C 07 D 411/00 C 07 D 473/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0382526 (J.A.F.) 16 August 1990, see the whole document	1-8,11-14,17

* Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
31-01-1992	17 FEB 1992
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT FFICE	Mme N. KUIPER

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 15 and 16 are directed to a method of treatment of the human body, the search has been based on the altributed effects of the compounds.

2. ☒ Claim numbers 18(compounds of cl. 1) because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. ☐ Claim numbers because they are dependant claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

CA 9100407
SA 53007

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 11/02/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0382526	16-08-90	US-A- 5047407	10-09-91
		AU-A- 4920190	16-08-90
		CA-A- 2009637	08-08-90
		JP-A- 3007282	14-01-91

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82